A Phase 3, randomized, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of UX007 in the treatment of movement disorders associated with Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

Protocol Number:	**UX007G-CL301**
Original Protocol:	**08 Dec 2015**
Amendment 1:	**24 Aug 2016**
Amendment 2:	**02 Feb 2017**
Amendment 3:	**10 July 2018**

Investigational Product:	UX007 (triheptanoin)
Indication:	Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)
IND Number:	118855
EudraCT Number:	2015-005536-17
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:	Darryl DeVivo, MD Columbia University Medical Center New York, NY USA 10032

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-CL301 Amendment 1

24 August 2016

Original Protocol UX007G-CL301 (dated 08 December 2015) has been modified by Amendment 1 to incorporate feedback from regulatory authorities and to modify or clarify certain study endpoints based on functional pilot studies and Glut1 DS patient interviews. Minor edits and typographical corrections have also been made. The major protocol changes which impact study design and conduct are summarized below:

1. **Primary Efficacy Endpoint: Disabling Paroxysmal Movement Events**
   The primary endpoint was revised to capture only movement disorder events that are disabling to the subject. Disabling events are defined in this study as any movement disorder events which limit one's physical functioning and ability to perform activities of daily living.

   Rationale: In capturing disabling events, the daily electronic Glut1 DS symptom diary was revised to support the Health Authority's suggestion to evaluate improvement in "ability to perform activities of daily living". This approach aims to evaluate changes that constitute clinically meaningful improvement in this patient population and also provides insight into the burden of illness caused by Glut1 DS.

2. **Secondary Efficacy Endpoints: 12 Minute Walk Test**
   The 12 Minute Walk Test was added as a secondary endpoint in the Schedule of Events (Table 2.2 and Table 2.3) and in Sections 6.1.2, 7.5.2.3, 7.5.5, and 7.6.3.

   Rationale: Walking impairments have been reported in patients with Glut1 DS. The 12MWT provides an objective assessment of walking capacity and endurance and was added to the study based on the Health Authority's advice to include a measure that evaluates change in performance of a functional outcome such as walking ability. The 12MWT was also selected as a measure of endurance to challenge the energy metabolism deficiency and assess potential treatment response.

3. **Secondary Efficacy Endpoints: Removal of SF-10/SF-12 and addition of PROMIS® item bank-based questionnaire**
   A Patient-Reported Outcomes Measurement Information System (PROMIS®)-based questionnaire was added as a secondary endpoint to the Schedule of Events and to Sections 6.1.2, 7.5.2.6, 7.5.5, and 7.6.3 to assess health-related quality of life.
   The SF-10 and SF-12 assessments were removed as secondary endpoints from the protocol.

Rationale: The PROMIS® item bank questionnaire was added as a patient-based assessment of health-related quality of life. Items are selected from the PROMIS® item to develop a questionnaire that evaluates concepts such as physical function, mobility, upper extremity function, fatigue, pain, and social health which have been reported as important impacts for Glut1 DS patients. SF-10 and SF-12 Health Surveys, which are more generalized assessments, were removed.

4. **Secondary Endpoints: CANTAB modification**
   The Cambridge Neuropsychological Test Automated Battery (CANTAB) was limited to certain study sites as noted in the Synopsis and in Sections 6.1.2, 7.5.2.7, 7.5.5, and 7.6.3.

   Rationale: To reduce the burden at study sites, the CANTAB will be administered at only select sites.

5. **Exploratory Endpoints: Removal of SARA and AIMS**
   The SARA and AIMS measures were removed as secondary endpoints from the Schedule of Events (Table 2.2 and Table 2.3) and from Sections 6.1.2, 7.5.2.6, 7.5.5, and 7.6.3.

   Rationale: In a functional pilot study conducted by the Sponsor, the SARA and AIMS assessments did not capture the episodic ataxia and abnormal involuntary movements experienced by this population in a clinic setting; therefore, these assessments were removed from the study.

6. **Exploratory Endpoint: Addition of Wearable Activity Monitor**
   An optional wrist-worn actigraphy device was added as an exploratory endpoint in the Schedule of Events (Table 2.2 and Table 2.3) and in Sections 6.1.3, 7.5.2.9, 7.5.5, and 7.6.3.

   Rationale: As fatigue, energy deficiencies, and disabling dyskinesia events commonly interfere with a patient's ability to participate in home and community activities, a wrist-worn actigraphy device has been added to evaluate the impact of Glut1 DS on activity levels in a real-life setting at select study sites where feasible.

7. **Exploratory Endpoint: Addition of Canadian Occupational Performance Measure**
   The Canadian Occupational Performance Measure (COPM) was added as an exploratory endpoint in the Schedule of Events (Table 2.2 and Table 2.3) and in Sections 6.1.3, 7.5.2.9, 7.5.5, and 7.6.3.

   Rationale: Following the Health Authority's suggestion to include measures that evaluate subjects' ability to perform activities of daily living and assess productivity, the Canadian Occupational Performance Measure (COPM) will be used to assess performance areas of self-care, leisure, and productivity.

8. **Schedule of Events:** The titration period was increased from one week to two weeks to allow subjects more time to reach the target dose. The Schedule of Events (Table 2.2 and Table 2.3) and other sections have been modified to reflect the increase in titration period and, subsequently, increased length of the crossover study.

   Rationale: By increasing the titration period, subjects will have more flexibility in the time period taken to reach the target dose.

9. **Exclusion Criteria:** A change was made in the Exclusion Criteria in the synopsis and in Section 7.3.2 to exclude subjects with feeding or nutritional issues that, in the opinion of the dietitian, may compromise their ability to consistently administer study drug.

   Rationale: Subjects with feeding issues may not be able to comply with regular dosing of study drug. The addition of this criterion will enable dietitians to exclude patients that are likely to be noncompliant with consistent study drug administration.

10. **Contraception Methods:** The list of examples of highly effective contraception methods was updated in Section 7.5.4.5.

    Rationale: This change was made to better clarify the acceptable methods of contraception in compliance with the Clinical Trial Facilitation Group (CTFG) advice.

11. **Record Retention:** Study records will be retained for at least 25 years after the end of the clinical trial as updated in Section 8.4.3.

    Rationale: The language in Section 8.4.3 was updated to reflect that study records will be retained for at least 25 years after the clinical trial.

12. **End of Study:** The synopsis (Duration of Treatment) and Sections 7.4.4.1 and 7.5.1 were updated to clarify that the End of Study is the last subject's Safety Follow-up Phone Call (30-35 days after the Final Dose).

    Rationale: This change was made to clearly define the End of Study.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL301 Amendment 2

02 February 2017

UX007G-CL301 Amendment 1 (dated 24 August 2016) has been modified by Amendment 2 to incorporate feedback from regulatory authorities:

1. **Safety Measures and General Assessments: Lipid Profile and Electrocardiogram**
   Lipid profile (Section 7.5.4.5) and electrocardiogram (Section 7.5.4.6) assessments were added as additional measures to evaluate the safety of UX007.

   Rationale: Regular lipid profile (subjects aged 18 or older) and ECG evaluations have been added for routine safety monitoring.

2. **Adverse Events: Clarification of Adverse Events**
   An additional statement has been added to the Adverse Events (Section 7.5.4.10) as well as to footnotes within the Schedules of Events (Table 2.2 and Table 2.3) to specify that increases in frequency or severity or changes in type of Glut1 DS associated symptoms (including seizures, movement disorders, behavioral abnormalities, and cognitive function) will be classified as adverse events.

   Rationale: Specific language was added to the Study Reference Manual and to the Protocol to clarify that the worsening of Glut1 DS associated symptoms will be appropriately recorded as adverse events.

3. **Selection of Doses: Inclusion of Maximum Dose**
   Section 7.4.4 has been modified to include the addition of a maximum daily UX007 dose.

   Rationale: While additional dosing information is available within the Pharmacy Manual, the Protocol has been amended to include this relevant information.

4. **Study Conduct: Clarification of Amendment Implementation**
   Section 8.1.1 has been modified to include Competent Health Authority approval prior to implementation of the protocol and substantial protocol amendments.

   Rationale: This statement has been included to document that substantial protocol amendments follow Ultragenyx standard operating procedures regarding Competent Health Authority approval.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL301 Amendment 3

10 July 2018

UX007G-CL301 Amendment 2 (dated 02 February 2017) has been modified by Amendment 3 to incorporate sequential testing procedure for the analysis of secondary endpoints, to add additional unscheduled clinic or phone visits, to add clarification to the assessments and schedule of events, and to continue evaluation of efficacy assessments during the Extension Period. The key changes to the study protocol are summarized below. Additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Regarding diary usage during Study Periods Treatment Period 1 and 2 and the Open-label Extension Phase, references to the "electronic daily Glut1 DS symptom diary" and "electronic study medication diary" have been replaced with a "daily Glut1 DS symptom diary" and "study medication diary" in Section 7.5.2.1, Section 7.4.7, and throughout the protocol.

   Rationale: The study will utilize a paper diary to capture movement disorders and daily consumption of study drug as a back-up in the event of an unexpected performance issue with the daily electronic diary during Treatment Period 1 and 2 and the Open Label Extension Phase. The paper diaries are not intended to be used during Screening or during the Run-in Period.

2. The order of study endpoints was modified in the synopsis and in Section 6.1 and the planned methods of analyses were updated in Section 7.6.3.

   Rationale: The study endpoint order and planned methods of efficacy analyses were changed to incorporate sequential testing procedure for the secondary endpoints.

3. In Section 7.1, the duration of the Run-in Period was modified to allow extension beyond the previously designated 6 weeks at the discretion of the Sponsor and the Principal Investigator.

   Rationale: This modification was made to allow flexibility should any study implementation issues preclude randomization following the 6-week Run-in Period as scheduled.

4. Language to allow unscheduled clinic visits or telephone calls at the site's discretion was added to the synopsis, Section 7.5.1, and Section 7.5.4.11.

   Rationale: Unscheduled visits and telephone calls were added to provide additional dietitian follow up and other study support as needed.

5. Language was added to Section 7.5.2.1 to specify that "Respondents should maintain ≥ 80% compliance with daily Glut1 DS symptom diary completion during the Run-in Period, Treatment Period 1, Washout Period and Treatment Period 2."

   Rationale: This modification was added to encourage sites to provide additional oversight to ensure that subjects complete Glut1 DS symptom diary.

6. Head circumference was added to vital sign assessment in Section 7.5.4.2.

   Rationale: This assessment was added to the protocol to be consistent with the Case Report Forms (CRFs) which are currently collecting this information as part of the scheduled clinic visits.

7. Changes to the Schedule of Events include the following:
   a. Study drug dispensation was added at Week 22 in Table 2.2 and in the text in Section 7.4.7.

      Rationale: this modification reflects that all subjects will receive UX007 at Week 22 (End of Treatment Period 2 Visit) to begin the open-label Extension Period.

   b. Dietary assessment and review of the 3-day diary was added to Baseline Visit 2 (Week 12) in Table 2.2.

      Rationale: Language was added for additional dietary assessment to ensure that subjects' diets remain isocaloric and well-balanced throughout the study.

   c. In Table 2.3, the End of Treatment Visit (Week 178) and Early Termination Visits were differentiated into separate columns.

      Rationale: This modification was performed to clarify the different assessments occurring during the Week 178 and Early Termination clinic visits.

d. The Cambridge Neuropsychological Test Automated Battery (CANTAB), 12 Minute Walk Test (12MWT), and the Patient/Caregiver Clinical Global Impression – Improvement (CGI-I) assessments were added to the Extension Clinic Visits and Early Termination Visit in Table 2.3.

Rationale: These assessments were added through the Extension Period for evaluation of long-term efficacy.

e. In Table 2.3, the "Suicide Ideation and Behavior Assessment" was changed to "Columbia Suicide Severity Rating Scale".

Rationale: This was a clarification made for consistent use of the nomenclature used in Table 2.2. Throughout the study, suicidal ideation is assessed via the Columbia Suicide Severity Rating Scale.

f. Review of the Study Medication Diary was added to clinic visits within Table 2.3.

Rationale: This clarification reflects the text in Section 7.5.1 which states that review of the Study Medication Diary is performed throughout the Extension Period.

g. Dietitian Consultation and Review of Study Medication Diary were made into separate assessments in Table 2.2.

Rationale: This clarification was to reflect that these assessments are completed by two different clinical functions (dietitian and study coordinator, respectively).

h. The frequency of neurological exams was modified within Table 2.3 to occur at every clinic visit (previously, only at Weeks 82 and 130).

Rationale: This clarification was made to reflect the text in Section 7.5.4.4 which states that neurological examinations occur at "subsequent clinic visits" throughout the study.

2 SYNOPSIS

TITLE OF STUDY:

A Phase 3, randomized, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of UX007 in the treatment of movement disorders associated with Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

PROTOCOL NUMBER:

UX007G-CL301

STUDY SITES:

Approximately 20 global sites

NUMBER OF SUBJECTS PLANNED:

The study will enroll approximately 40 subjects who experience disabling paroxysmal movement disorders

PHASE OF DEVELOPMENT:

Phase 3

RATIONALE:

Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS) is a rare, severely debilitating disease characterized by seizures, developmental delay, and movement disorders. 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 brain's primary source of energy, this disorder results in a chronic state of cerebral energy deficiency. Current management of Glut1 DS consists of the ketogenic diet (KD) which has been shown to be effective in controlling seizures associated with Glut1 DS (Pong et al. 2012, Pearson et al. 2013). However, there is less evidence supporting the effects of KD on movement disorders experienced by Glut1 DS patients.

Symptoms can vary considerably with respect to both frequency and severity (Pearson et al. 2013). The clinical presentation of Glut1 DS may manifest as epilepsy, cognitive/developmental delays, movement disorders, or an assortment of all of these elements (Klepper et al. 2016).
The movement disorders associated with Glut1 DS are well documented and occur across the patient spectrum. Pearson et al (2013) describe abnormal gait (typically ataxic or spastic-ataxic gait), dystonia and chorea as common motor disorders observed in Glut1 DS patients, with most patients exhibiting more than one motor abnormality (Pearson et al. 2013). The range of movement disorders that Glut1 DS patients experience may also be continuous and/or paroxysmal in nature. Paroxysmal symptoms are commonly triggered by fasting and/or exercise, as well as other provoking factors, suggesting that these are energy dependent manifestations and may be responsive to the delivery of energy substrates to the brain. In a qualitative research study, patients and caregivers were asked to report the types of movement disorders experienced and to describe any disability associated with the movement disorder events. Participants reported a wide variety of episodic movement disorders and difficulty performing many activities during the movement disorder events. Participants described significant motor problems with mobility, including impaired walking/running ability and trouble with balance, including falls. Caregivers/patients also reported difficulty with activities from movement disorders affecting their upper extremities, including problems with self-care functions such as dressing and feeding, and fine motor function

e.g. writing. These movement disorders also often limited participation in sports and school activities. In addition to difficulty performing motor tasks, caregivers and patients described the impact of the movement disorders on social and emotional aspects of life, including embarrassment, social isolation and difficulty making friends (reference: data on file).

In a recent, open-label Phase 2 study, paroxysmal manifestations improved significantly (p=0.028) in six evaluable patients, in response to treatment with triheptanoin (Mochel et al. 2015). Subjects were asked to record all paroxysmal non-epileptic manifestations including motor (e.g., hyperkinetic movement disorders, speech disorder, and limb weakness) and non-motor (e.g. fatigue, headache, sleep disturbance, disorientation, and mood disorder) events prior to and post treatment with triheptanoin. The numbers of motor and non-motor events were markedly reduced during treatment with triheptanoin followed by an increase in these paroxysmal events when triheptanoin treatment was subsequently withdrawn. Subjects were also asked to score changes in their clinical condition since the start of triheptanoin therapy. Patient-reported clinical global impression of improvement (CGI-I) scores demonstrated a clear improvement after the triheptanoin treatment period followed by worsening of their condition on withdrawal of treatment, tracking the temporal profile of changes in frequency of paroxysmal manifestations. Physicians also rated the severity of the study subjects based on their clinical experience with Glut1 DS and considered these subjects, in whom paroxysmal events were the primary manifestation of the disease, to be moderately to markedly ill. The most common motor manifestations included muscle stiffness, movement disorder, and weakness. All of these symptoms decreased in frequency when treatment with triheptanoin was initiated. During Baseline in the Mochel study, functional ^{31}P-nuclear magnetic resonance spectroscopy (f-MRS) showed no change in Pi/PCr ratio during brain activation in the Non KD population. After the UX007 treatment period, the bioenergetics profile normalized; repeated measures ANOVA (p= 0.014), with an increase in Pi/PCr ratio during visual stimulation and a significant decrease during recovery (p= 0.021). Increased Pi/PCr ratio during brain activation reflected a proportional elevation of ADP, allowing increased mitochondrial ATP production with UX007. After treatment withdrawal, the f-MRS profile reverted to the baseline levels (Mochel et al. 2015). These data suggest that UX007 improves energy availability for brain function.

The severity of the motor symptoms can range from mild to quite severe. In the latter cases, the dystonic postures may involve axial or orobuccal musculature and be accompanied by dysphoria and inconsolable crying (Pons et al. 2010), suggesting a profound effect on quality of life.
The non-motor manifestations may also be very disturbing to patients. In the Mochel study, fatigue, headache and sleep disturbance were the most common non-motor manifestations.
The total score of non-motor manifestations was improved with the initiation of UX007.
Paroxysmal non-motor manifestations may also include confusion, lethargy, somnolence, paroxysmal episodes of pain, drowsiness, dysphoria, and weakness (Pons et al. 2010, Urbizu et al. 2010, Gras et al. 2014, Roze et al. 2015). In one series of 33 patients, headaches occurred in 6% and cyclic vomiting was reported in 46% (Ito et al. 2015). All may detract significantly from the day-to-day function and quality of life of the patient and potentially also for the family caregiver. Paroxysmal manifestations of Glut1 DS, both motor and non-motor, may therefore be considered a significant unmet medical need for this patient population.

The proposed mechanism for both paroxysmal motor and non-motor manifestations appears to be related to a brain energy deficit related to energy expenditure (Weber et al. 2008, Wang et al. 2012).

Since glucose transfer into the brain relies on serum glucose levels, conditions leading to transient serum hypoglycemia such as fasting or exercise would be expected to result in a variety of

paroxysmal manifestations. The types of paroxysmal manifestations depend on the area of the brain that is relatively energy deficient. For example, failure to meet the energy demand of the growing cortex in infancy likely results in seizures; cerebellar energy deprivation would lead to worsening ataxia; and energy loss in the basal ganglia (along with thalamocortical hypometabolism) would result in paroxysmal movement disorders, such as dystonia, chorea, or tremors (Pons et al. 2015, Akman et al. 2015).

There are currently no approved therapies for the movement disorder events associated with Glut1 DS. Triheptanoin, a triglyceride composed of three heptanoate (C7 fatty acid) esters, 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. The proposed Phase 3 study is designed to assess the efficacy and safety of UX007 (triheptanoin) in reducing the frequency of disabling paroxysmal movement disorder events in Glut1 DS patients. By focusing on disabling movement disorder events, the study will capture clinically meaningful events which limit physical functioning and activities of daily living. This study will assess patients who are not currently treated with KD, as this diet may affect some energy-dependent symptoms in Glut1 DS. The study will also evaluate the pharmacokinetics (PK) of energy-containing metabolites and correlate these to the potential treatment effects.

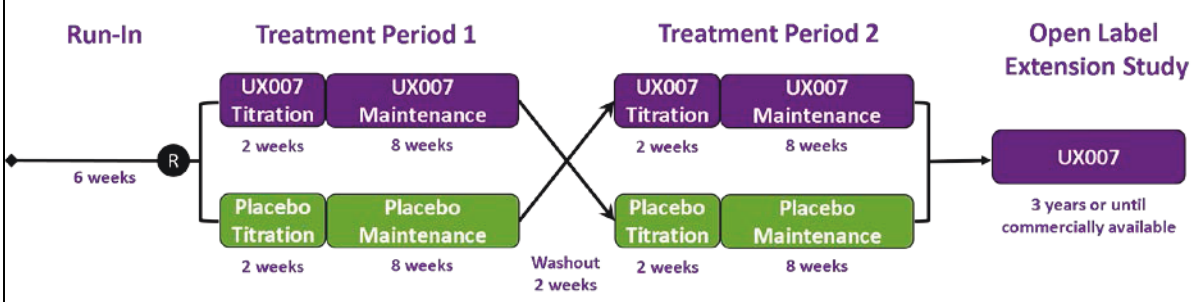
STUDY DESIGN AND METHODOLOGY:

UX007G-CL301 is a randomized, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of UX007 in Glut1 DS. The study will enroll approximately 40 pediatric, adolescent, and adult subjects who are not on KD and are having disabling paroxysmal movement disorders. A movement disorder event is defined in this study as a period of time when the subject experiences one or more movement disorder symptoms, including symptoms that are experienced during a movement disorder event alone or significant worsening of continuous movement disorders. In this study, movement disorder events are defined as disabling if they affect or limit a subject's activities of daily living.

During the 6-week Run-in Period, subjects will record disabling paroxysmal movement disorder events in a daily electronic Glut1 DS symptom diary; if the minimum criterion for number of events is not met or subjects complete <80% of the daily electronic Glut1 DS symptom diary, the subject will be considered a screen failure and will not be randomized. Individuals may be allowed to rescreen, at the discretion of the Principal Investigator, subject to approval by the Medical Monitor. At the discretion of the Sponsor and Principal Investigator, the Run-In Period may be extended beyond 6 weeks.

At the end of the Run-in Period, eligible subjects will be randomized (1:1 ratio) to one of two treatment sequences (UX007/placebo or placebo/UX007). At Randomization, subjects will begin a 10-week double-blind Treatment Period 1. Treatment Period 1 will consist of a 2-week titration period and an 8-week Maintenance Period. At the end of Treatment Period 1, subjects will discontinue treatment and begin a 2-week washout period to minimize any potential carryover effect. Subjects will crossover to the second randomized, double-blind treatment assignment (placebo to UX007, UX007 to placebo) for an additional 10 weeks during Treatment Period 2. Treatment Period 2 will consist of a 2-week titration period and an 8-week Maintenance Period. At the end of the blinded crossover period (Week 22), all active subjects will have the option of rolling into the open-label Extension Period, to continue UX007 treatment for up to 3 years or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator, the study is terminated, or until commercial availability of the study drug in a subject's region, whichever occurs first. Long-term safety and maintenance of effect of UX007 will be assessed during the open-label Extension Period. A study schematic is provided in Figure 2.1. A Safety Follow-up Phone Call will be conducted 30-35 days after the last dose of UX007G-CL301 study drug.

Figure 2.1: UX007G-CL301 Study Schematic



OBJECTIVES:

The primary objective of the study is to:

- Evaluate the efficacy and safety of UX007 in the treatment of disabling paroxysmal movement disorders associated with Glut1 DS

ENDPOINTS:

Endpoints will be evaluated for UX007 and placebo treatment.

Primary Endpoint

The primary endpoint is the frequency of disabling paroxysmal movement disorders captured as movement disorder events observed during the Maintenance Period of treatment, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary.

Secondary Endpoints

- Duration of disabling paroxysmal movement disorder events observed during the Maintenance Period of treatment, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary
- Walking capacity and endurance, as determined by the distance walked in 12 minutes during the 12 Minute Walk Test (12MWT)
- Patient/caregiver global impression of change in clinical status using the Clinical Global Impression – Improvement (CGI-I)
- Health-related quality of life assessing physical function, mobility, upper extremity function, fatigue, pain and social health using a PROMIS®-based questionnaire
- Cognitive function as measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB) (assessed at select sites)

Exploratory Endpoints

- Self-care, productivity, and leisure performance assessed by the Canadian Occupational Performance Measure (COPM)
- Physician global impression of change in clinical status using the Clinical Global Impression – Severity scale (CGI-S) and Clinical Global Impression – Improvement (CGI-I)
- Activity levels as measured by a wrist-worn actigraphy device at select study sites, where feasible. Endpoints include mean daytime activity, mean nighttime activity, and percent time in moderate or higher intensity activity
- Frequency and duration of disabling paroxysmal movement disorder events over time throughout the three-year open-label extension period
- PK data for UX007 metabolites

Safety Endpoints

- Adverse events, including the subject incidence of adverse events (AEs), treatment related AEs, serious adverse events (SAEs), AEs leading to discontinuation and fatal AEs
- Clinically significant changes in vital signs, clinical laboratory test results, and electrocardiogram (ECG)
- Change in suicidal ideation & behavior assessment as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)

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, aged ≥6 years old at the time of informed consent
3) At least 8 disabling paroxysmal movement disorder events in the 12 weeks prior to the Screening, by subject or caregiver report

   OR

   At least 6 disabling paroxysmal movement disorder events in any 6 consecutive week period, over the last 12 week period prior to the Screening, by subject or caregiver report
4) At least 4 disabling paroxysmal movement disorder events in the first 6 weeks of Run-in Period, reported in the daily electronic Glut1 DS symptom diary
5) ≥80% compliance with daily electronic Glut1 DS symptom diary completion during the Run-in Period
6) Not on KD, modified KD, or ketosis-inducing modified-fat diet for at least 3 months prior to Screening
7) Plasma level of beta-hydroxybutyrate (BHB) ≤ 1 mmol/L (non-fasting) at Screening
8) Provide written or verbal assent (if possible) and written informed consent by the patient (if an adult), or by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures
9) Must, in the opinion of the Investigator, be willing and able to complete key aspects of the study and be likely to complete the 22-week, placebo-controlled, treatment period
10) Patient (or caregiver) must, in the opinion of the Investigator, be able to comply with accurate completion of the study daily Glut1 DS symptom diary
11) Females of child-bearing potential must have a negative urine pregnancy test at Screening and Baseline and be willing to have additional pregnancy tests during the study. Females considered not to be of childbearing potential include those who have not experienced menarche, are post-menopausal (defined as having no menses for at least 12 months without an alternative medical cause) or are permanently sterile due to total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
12) Participants of child-bearing potential or fertile males with partners of child-bearing potential who are sexually active must consent to use a highly effective method of contraception as determined by the site Investigator from the period following the signing of the informed consent through 30 days after last dose of study drug

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

1) Any known hypersensitivity to triheptanoin or safflower oil that, in the judgment of the Investigator, places the subject at increased risk for adverse effects
2) Prior use of triheptanoin within 30 days prior to Screening

3) History of, or current suicidal ideation, behavior and/or attempts per C-SSRS at Screening or Baseline
4) Pregnant and/or breastfeeding an infant at Screening or Baseline
5) Participants unwilling or unable to discontinue use of a prohibited medication or other substance that may confound study objectives (Section 7.4.6.1 [MCT oil, barbiturates, pancreatic lipase inhibitors, KetoCal or other KD supplements, and/or KD])
6) Glut1 DS treatment regimen, including AEDs, should be stable for at least 30 days prior to Screening
7) Use of any investigational product (drug, medical food, or supplement, including medium chain triglyceride [MCT] oil, including coconut oil) within 30 days prior to Screening
8) 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
9) Feeding or nutrition that, in the opinion of the dietitian, potentially affects consistent administration of study drug

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION:

UX007 (triheptanoin) is a liquid, intended for oral (PO) administration. UX007 is a colorless to yellow oil supplied in 1 L round, translucent high-density polyethylene (HDPE) or 1 L round amber colored glass bottles. Subjects will be dosed according to an age- and weight-based strategy (Table 2.1), up to a maximum daily administration of 130g. For subjects within 25% predicted BMI, actual body weight will be used to calculate the appropriate dose per the subject's age category. Adjusted body weight will be used for subjects with greater than 25% predicted BMI, to account for metabolic activity found in adipose tissue versus lean muscle. Adjusted body weight will be calculated in kilograms, using the following formula:

Formula 1# Adjusted Body Weight = Ideal Body Weight + [25% × (Actual Body Weight − Ideal Body Weight)]

UX007 dosing will be initiated using a 2-week titration schedule until the subject has reached his/her target total daily dose. If a subject has not reached the target total daily dose by the end of the 2-week titration period, dose titration should continue until the maximum tolerated dose is reached. For detailed information regarding dosing and titration, please refer to the Study Reference Manual.

Table 2.1: Age-based UX007 Target Total Daily Dose

Age Range	UX007 dose (g/kg/day) that is estimated equivalent to 30% total caloric intake
6 – 9 Years	2.5
10 – 14 Years	2
15 – 20 Years	1.5
21 and Over	1.2

The total daily dose will be divided into 4 equal doses mixed with food or drink (or formula, as appropriate), and administered PO or by gastronomy tube at breakfast, lunch, dinner, and before bed. The dose may be divided into smaller more frequent doses with food or drink as needed. The il should not be taken without thoroughly mixing with food or drink. The dose should not be adjusted due to changes in age and/or weight during Periods 1 and 2.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Placebo will consist of safflower oil matching the attributes of UX007 oil. Dose level, titration, 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 approximately 3.5 years, consisting of a 6-week Run- in Period, a 22-week placebo-controlled, crossover Treatment Period, followed by an optional, open-label Extension Period. All subjects who have completed the 22-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. A Safety Follow-up Phone Call will be conducted 30-35 days after the last dose of UX007G-CL301 study drug. The last subject's Safety Follow-up Phone Call is the End-of-Study Time Point.

CRITERIA FOR EVALUATION:

Primary and Secondary Efficacy Assessments:

Disabling Paroxysmal Movement Disorders

- Subject Daily Glut1 DS symptom Diary: An event-based Glut1 DS symptom diary will allow the subject/caregiver to capture quantitative and qualitative aspects of disabling paroxysmal movement disorder events

Functional Outcome: Walking Capacity

- 12 Minute Walk Test (12MWT): The 12MWT is a variation of the 6MWT used to assess walking capacity and endurance as a functional outcome.

Health-related Quality of Life

- The Patient Reported Outcomes Measurement Information System (PROMIS®): A patient/proxy reported questionnaire selected from the PROMIS®-item bank to assess physical function, mobility, upper extremity function, fatigue, pain and social health.

Clinical Status: Patient Impression of Global Symptom and Disease Severity

- Patient impression of severity and change: The global impression of disease severity (using a 4-point Likert scale) at the start of the study and the degree of change in clinical status (CGI-I) as assessed by the patient/caregiver (7-point Likert scale) since the start of the study

Cognitive Function

- Cambridge Neuropsychological Test Automated Battery (CANTAB): Neuropsychological function measured using a standardized, computerized battery of tests designed to assess cognitive domains relevant to Glut1 DS subjects such as attention and memory tests. CANTAB will be performed at select study sites.

Exploratory Outcome Measures:

Clinical Status: Physician Impression of Global Symptom and Disease Severity

- Physician impression of severity and change: Physicians will rate disease severity at Baseline (CGI-S) and continue to rate severity for the duration of the study using a 4-point Likert scale. Physicians will also record the degree of change in clinical status (CGI-I) using a 7-point Likert scale at post treatment visits.

Pharmacokinetic analysis of UX007 metabolites

- PK Analysis: a summary of PK analysis data and descriptive statistics will be completed

Activity Levels

- Actigraphy Device: A wrist-worn actigraphy device will assess the impact of Glut1 DS on activity levels during the last 10 days of the Run-In Period, the last 10 days of Treatment Period 1 and the last 10 days of Treatment Period 2. Endpoints include mean daytime activity, mean night time activity, and percent time in moderate or higher intensity activity. Actigraphy device will be used at select study sites, where feasible.

Qualitative Assessment

- Canadian Occupational Performance Measure: COPM will assess the impact of Glut1 DS on performance areas of self-care, productivity, and leisure.

Safety Assessments:

- Incidence, frequency, severity, and relatedness of AEs and SAEs, including clinically significant changes from Baseline to scheduled time points in in vital signs, clinical laboratory test results, and ECG
- Vital signs, weight, physical examination
- Pregnancy testing, suicidal ideation, via the Columbia Suicide Severity Rating Scale (C-SSRS)

STATISTICAL METHODS:

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

Sample Size:

Based on the targeted patient population and eligibility criteria, it is estimated that the subjects receiving placebo will have a mean frequency of 8 disabling paroxysmal movement disorder events per 4 weeks, while subjects receiving UX007 will have a mean frequency of 4 disabling paroxysmal movement disorder events per 4 weeks, and a standard deviation of the difference of 7.4. A total sample size of 40 subjects (20 subjects in each treatment sequence) will have at least 85% power to detect such difference between UX007 and placebo groups. This sample size assumption incorporates a projected discontinuation rate of 15%.

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 they actually received for the safety analysis.

Efficacy Analysis:

The primary analysis will compare the frequency of paroxysmal movement disorders captured as disabling movement disorder events (normalized to a 4 week rate) observed during the Maintenance Period of treatment with UX007 to the frequency of disabling movement disorders captured as movement disorder events (normalized to a 4 week rate) observed during the Maintenance Period of treatment with placebo, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary.

The primary endpoint will be analyzed based on the efficacy analysis set using a weighted ANCOVA model, with study baseline frequency of movement disorder as a covariate, treatment sequence, treatment group and period as fixed effects, and a random effect for subject within the sequence. When there is strong evidence suggesting that the normality assumption is not met, Wilcoxon rank-sum test will be considered as the primary analysis to assess the primary endpoint. The specific model will be defined in the SAP. The hypothesis that there is no difference in mean frequency of disabling paroxysmal movement disorder events per 4 weeks between treatment groups will be tested at the α=0.05 (2-sided) level.

For change-from-baseline efficacy endpoints, the baseline will be the last measurement taken prior to or on the first dose date of the first period for computation of the change from baseline value. The baseline measurement will be recorded before the dose is administered.

If the primary analysis for the primary efficacy endpoint is statistically significant, then a sequential testing strategy will be implemented for selected secondary efficacy endpoints in the following order:

- Duration of disabling paroxysmal movement disorder events
- Change from Baseline in 12MWT distance
- Patient/caregiver global impression of change in clinical status using the Clinical Global Impression – Improvement (CGI-I)

Safety Analysis:

All treatment emergent AEs (TEAEs) will be included in the analysis. Subject incidence of TEAE will be summarized by actual treatment received using the safety analysis set. Subject incidence of TEAE resulting in death, discontinuation and serious TEAE by actual treatment received will also be summarized. For C-SSRS, the percentage of subjects reporting any treatment emergent suicidal ideation and any treatment emergent suicidal behavior will be summarized descriptively by actual treatment received and visit week, respectively.

Table 2.2: Schedule of Events (Screening; Run-in; Period 1; Washout; and Period 2)

ASSESSMENT	Screening Visit Week -6	6-week Run-in Period	TREATMENT PERIOD 1			2-week Washout	TREATMENT PERIOD 2		
			Baseline 1	Phone Visits 1, 2, and 3	End of Treatment 1		Baseline 2 (End of Washout)	Phone Visits 4, 5, and 6	End of Treatment 2
			Week 0 (± 3 days)	Weeks 2, 4, and 6 (± 3 days)	Week 10 (± 3 days)		Week 12 ±3 days	Weeks 14, 16, and 18 (± 3 days)	Week 22 (± 3 days)
Informed Consent	X								
Inclusion/Exclusion Criteria	X		X						
Medical History	X								
SAFETY ASSESSMENTS									
Vital Signs	X		X		X		X		X
Physical Examination	X		X		X		X		X
Neurological Examination			X		X		X		X
Height	X		X		X		X		X
Weight	X		X		X		X		X
Columbia Suicide Severity Rating Scale (C-SSRS)[1]	X		X		X		X		X
Clinical Laboratory Tests[2]	X		X		X		X		X
Electrocardiogram (ECG)			X		X				X
Urine Pregnancy Test (If appropriate)[3]	X		X		X		X		X
Adverse Events[4, 5]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

ASSESSMENT	Screening Visit Week -6	6-week Run-in Period	TREATMENT PERIOD 1			2-week Washout	TREATMENT PERIOD 2		
			Baseline 1	Phone Visits 1, 2, and 3	End of Treatment 1		Baseline 2 (End of Washout)	Phone Visits 4, 5, and 6	End of Treatment 2
			Week 0 (± 3 days)	Weeks 2, 4, and 6 (± 3 days)	Week 10 (± 3 days)		Week 12 ±3 days	Weeks 14, 16, and 18 (± 3 days)	Week 22 (± 3 days)
EFFICACY ASSESSMENTS									
Daily Glut1 DS Symptom Diary Training	X								
Daily Glut1 Symptom DS Diary Review			X	X	X		X	X	X
Daily Glut1 DS Symptom Diary Completion [6]		X	X	X	X	X	X	X	X
12MWT	X		X		X		X		X
CANTAB[7]	X		X		X		X		X
PROMIS® Questionnaire			X		X		X		X
Patient: Clinical Global Impression of Severity			X						
Patient: Clinical Global Impression of Improvement					X		X		X
Physician: Clinical Global Impression of Severity			X		X		X		X
Physician: Clinical Global Impression of Improvement					X		X		X

ASSESSMENT	Screening Visit Week -6	6-week Run-in Period	TREATMENT PERIOD 1			2-week Washout	TREATMENT PERIOD 2		
			Baseline 1	Phone Visits 1, 2, and 3	End of Treatment 1		Baseline 2 (End of Washout)	Phone Visits 4, 5, and 6	End of Treatment 2
			Week 0 (± 3 days)	Weeks 2, 4, and 6 (± 3 days)	Week 10 (± 3 days)		Week 12 ±3 days	Weeks 14, 16, and 18 (± 3 days)	Week 22 (± 3 days)
Canadian Occupational Performance Measurement			X		X		X		X
Actigraphy Training[8]	X								
Actigraphy[8]		X			X				X
SPECIALTY LABORATORY ASSESSMENTS									
UX007 Metabolites[9]			X		X		X		X
BHB for ketosis detection	X		X		X		X		X
TREATMENT & DIETARY ASSESSMENTS									
Dietary Assessment and Consultation & Training on 3-day Diet Diary	X								
Dietary Assessment& Review of 3-day Diet Diary			X		X		X		X
Dietitian Consultation			X	X	X		X	X	X
Daily Study Medication Diary[6]			X	X	X		X	X	X
Review of Study Medication Diary			X	X	X		X	X	X
Daily Treatment with IP/Placebo			X	X	X		X	X	X

ASSESSMENT	Screening Visit Week -6	6-week Run-in Period	TREATMENT PERIOD 1			2-week Washout	TREATMENT PERIOD 2		
			Baseline 1	Phone Visits 1, 2, and 3	End of Treatment 1		Baseline 2 (End of Washout)	Phone Visits 4, 5, and 6	End of Treatment 2
			Week 0 (± 3 days)	Weeks 2, 4, and 6 (± 3 days)	Week 10 (± 3 days)		Week 12 ±3 days	Weeks 14, 16, and 18 (± 3 days)	Week 22 (± 3 days)
Dispense Study Drug			X				X		X[10]
Treatment Compliance & Accountability				X	X			X	X

1 Suicidal ideation and behavior will be assessed in subjects who are ≥ 10 years of age at each visit
2 For subjects ≥ 18 years old, 1ipid profile blood tests (LDL, HDL, total cholesterol, and triglycerides) will be assessed at Baseline 1 (Week 0), End of Treatment 1 (Week 10), and End of Treatment 2 (Week 22) after an overnight fast (8-12 hours).
3 For females of child-bearing potential
4 Plasma metabolite samples will be collected at time of SAE, if feasible
5 The definition of an AE also encompasses any increases in frequency or severity, or changes in type of Glut1 DS-associated symptoms, including but not limited to seizures, movement disorders, behavioral abnormalities, cognitive function, etc.
6 Glut1 DS symptom diary and study medication diary will be completed daily by the patient/caregiver. Review of the daily diaries will be performed at clinic or phone visits as indicated (or more frequently if needed)
7 CANTAB will be performed at select study sites
8 An actigraphy device will be worn on the last 10 days of the Run-in Period, the last 10 days of Treatment Period 1, and the last 10 days of Treatment Period 2 at select study sites, where feasible. Training for the actigraphy device will be provided at the Screening Visit.
9 Blood for plasma at Baseline Visits will be collected pre-dose. Blood for plasma at End of Treatment visits 1 and 2 will be collected approximately 90 minutes post dose.
10 Beginning at Week 22, all subjects will be dispensed UX007 for the open-label Extension Period

Table 2.3: Schedule of Events (Extension and Safety Follow-up)

ASSESSMENT	EXTENSION		END OF TREATMENT VISIT	EARLY TERMINATION VISIT	SAFETY FOLLOW-UP
	Extension Visits	Extension Phone Visits	End of Treatment Visit	Early Termination Visit	Follow-up Phone Call[10]
	Weeks 34, 58, 82, 106, 130, 154 (± 2 weeks)	Weeks 26, 30, 46, 70, 94, 118, 142 (± 2 weeks)	Week 178 (±2 weeks)	Final Dose (+4 weeks)	30-35 Days after Final Dose
SAFETY ASSESSMENTS					
Vital Signs	X		X	X	
Physical Examination	X		X	X	
Neurological Examination	X		X	X	
Height[1]	X		X	X	
Weight	X		X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)[2]	X		X	X	
Clinical Laboratory Tests[3]	X		X	X	
Electrocardiogram (ECG)[4]	Weeks 58, 106, and 154 Only			X[4]	
Urine Pregnancy Test (If appropriate)[5]	X		X	X	
Adverse Events[6]	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
EFFICACY ASSESSMENTS					
Daily Glut1 DS Symptom Diary review	X	X	X	X	
Daily Glut1 DS Symptom Diary completion[7]	X	X	X	X	
12MWT	X		X	X	
CANTAB[8]	X		X	X	

ASSESSMENT	EXTENSION		END OF TREATMENT VISIT	EARLY TERMINATION VISIT	SAFETY FOLLOW-UP
	Extension Visits	**Extension Phone Visits**	**End of Treatment Visit**	**Early Termination Visit**	**Follow-up Phone Call[10]**
	Weeks 34, 58, 82, 106, 130, 154 (± 2 weeks)	**Weeks 26, 30, 46, 70, 94, 118, 142 (± 2 weeks)**	**Week 178 (±2 weeks)**	**Final Dose (+4 weeks)**	**30-35 Days after Final Dose**
Patient: Clinical Global Impression of Improvement	X		X	X	
PROMIS® Questionnaire	X		X	X	
Physician: Clinical Global Impression of Severity	X		X	X	
Physician: Clinical Global Impression of Improvement	X		X	X	
Canadian Occupational Performance Measure	X		X	X	
SPECIALTY LABORATORY ASSESSMENTS					
UX007 Metabolites[9]	Week 34 Only[9]				
BHB for ketosis detection	X		x	X	
In-clinic dose	Week 34 Only[9]				
TREATMENT & DIETARY ASSESSMENTS					
Dietary Assessment/ Consultation & Review of 3-day Diet Diary	X		X	X	
Daily Study Medication Diary[7]	X	X			
Review of Study Medication Diary	X		X	X	
Daily Treatment with IP	X	X			
Dispense Study Drug	X				

ASSESSMENT	EXTENSION		END OF TREATMENT VISIT	EARLY TERMINATION VISIT	SAFETY FOLLOW-UP
	Extension Visits	**Extension Phone Visits**	**End of Treatment Visit**	**Early Termination Visit**	**Follow-up Phone Call[10]**
	Weeks 34, 58, 82, 106, 130, 154 (± 2 weeks)	**Weeks 26, 30, 46, 70, 94, 118, 142 (± 2 weeks)**	**Week 178 (±2 weeks)**	**Final Dose (+4 weeks)**	**30-35 Days after Final Dose**
Treatment Compliance & Accountability	X	X	X	X	

1 Height only to be collected in the extension period for subjects under the age of 20
2 Suicidal ideation and behavior will be assessed in subjects who are ≥ 10 years of age at each visit
3 For subjects ≥ 18 years old, 1ipid profile blood tests (LDL, HDL, total cholesterol, and triglycerides) will be at clinic extension visits after an overnight fast (8-12 hours).
4 ECG will be performed at Weeks 58, 106, 154 during the Extension Period (or Early Termination, if applicable). ECG will not be performed at Early Termination visit if the assessment was conducted within 3 months of termination.
5 For females of child-bearing potential
6 The definition of an AE also encompasses any increases in frequency or severity, or changes in type of Glut1 DS-associated symptoms, including but not limited to seizures, movement disorders, behavioral abnormalities, cognitive function, etc.
7 Glut1 DS symptom diary and study medication diary will be completed by the patient/caregiver. Review of the daily diaries will be performed at clinic or phone visits as indicated.
8 CANTAB will performed at select study sites.
9 Blood for plasma metabolites will be collected at the Week 34 visit only (pre-dose (within 15 minutes) and at [± 5 minutes] 30, 90, and 120 minutes post dose).
10 Safety-Follow-up Phone Call to be conducted 30-35 days after last dose of UX007G-CL301study drug, even in cases of Early Termination. The site personnel will initiate this safety follow-up telephone call to collect information on any ongoing or new AEs, serious adverse events (SAEs), and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

12MWT	12 Minute Walk Test
ADA	Americans with Disabilities Act
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
APBD	adult polyglucosan body disease
AST	aspartate aminotransferase
BHB	beta-hydroxybutyrate
BHP	beta-hydroxypentanoic 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
COPM	Canadian Occupational Performance Measure
CSF	Cerebral spinal fluid
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
EC	Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture
EEG	Electroencephalogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAOD	fatty acid oxidation disorders
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GLP	Good Laboratory Practice
Glut1	glucose transporter type 1
Glut1 DS	glucose transporter type 1 deficiency syndrome
GMP	Good Manufacturing Practice
GSD II	glycogen storage disease type II

HDL	high density lipoprotein
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IST	Investigator-sponsored Trial
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
KD	ketogenic diet
LC-FAOD	long-chain fatty acid oxidation disorders
LDL	low density lipoprotein
L	liter
MCT	medium chain triglyceride
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
PED	paroxysmal exertional dyskinesia
PK	Pharmacokinetic
PO	oral, by mouth, *per os*
PROMIS®	Patient Reported Outcomes Measurement Information System
PT	Preferred Term
RBC	red blood cell
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
TCA	tricarboxylic acid
TK	Toxicokinetic
US	United States
UX007	Investigational Product/study drug, triheptanoin

WBC	white blood cell
WHO	World Health Organization

Definition of Terms

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

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

5 INTRODUCTION

Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS) is a rare, severely debilitating disease characterized by seizures, developmental delay, and movement disorders. Glut1 DS is caused by a mutation in the solute carrier family 2, member 1(*SLC2A1)* gene, encoding the Glut1 protein responsible for transporting glucose across the blood brain barrier. Because glucose is the primary source of energy for the brain, this disorder results in a chronic state of cerebral energy deficiency.

5.1 Overview of Glucose Transporter Type 1 Deficiency Syndrome

Glut1 DS is a rare disease with an estimated birth incidence of 1:90,000 (Coman et al. 2006). This birth incidence translates to an estimated prevalence of ~8,500 in the US and Europe. Most commonly Glut1 DS is inherited in an autosomal dominant manner; approximately 90 % of individuals with autosomal dominant Glut1 DS have a *de novo* heterozygous mutation in *SLC2A1*, and about 10% have a clinically-affected parent (Wang et al. 1993-2015). Autosomal recessive transmission has also been described in rare cases.

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

Symptoms can vary considerably with respect to both frequency and severity (Pearson et al. 2013). The clinical presentation of Glut1 DS may manifest as epilepsy, cognitive/developmental delays, movement disorders, or an assortment of all of these elements (Klepper et al. 2016). Recently, there has been a dramatic expansion in the range of clinical syndromes that are recognized to occur with Glut1 DS including patients with milder forms of epilepsy, patients with non-epileptic syndromes characterized by both persistent and paroxysmal movement disorders, and patients with varying degrees of cognitive impairment (Pearson et al. 2013).

Movement disorders associated with Glut1 DS are well documented and occur across the patient spectrum. Pearson et al (2013) describe abnormal gait (typically ataxic or spastic-ataxic gait), dystonia and chorea as common motor disorders observed in Glut1 DS patients, with most patients exhibiting more than one motor abnormality (Pearson et al. 2013). The range of movement disorders that Glut1 DS patients experience may also be continuous and/or paroxysmal in nature. Paroxysmal symptoms are commonly triggered by fasting and exercise, amongst other potential provoking factors, suggesting that these are energy dependent manifestations and may be responsive to the delivery of energy substrates to the brain.

The non-motor manifestations may also be very disturbing to patients. In the Mochel study, fatigue, headache and sleep disturbance were the most common non-motor manifestations. The total score of non-motor manifestations was improved with the initiation of UX007. Paroxysmal non-motor manifestations may also include confusion, lethargy, somnolence, paroxysmal episodes of pain, drowsiness, dysphoria, and weakness (Pons et al. 2010, Urbizu et al. 2010, Gras et al. 2014, Roze et al. 2015). In one series of 33 patients, headaches occurred in 6% and cyclic vomiting was reported in 46% (Ito et al. 2015) All may detract significantly from the day-to-day function and quality of life of the patient and potentially also for the family caregiver. Paroxysmal manifestations of Glut1 DS, both motor and non-motor, may therefore be considered a significant unmet medical need for this patient population.

The proposed mechanism for both paroxysmal motor and non-motor manifestations appears to be related to a brain energy deficit related to energy expenditure (Weber et al. 2008, Wang et al. 2012).

Since glucose transfer into the brain relies on serum glucose levels, conditions leading to transient serum hypoglycemia such as fasting or exercise would be expected to result in a variety of paroxysmal manifestations. The types of paroxysmal manifestations depend on the area of the brain that is relatively energy deficient. For example, failure to meet the energy demand of the growing cortex in infancy likely results in seizures; cerebellar energy deprivation would lead to worsening ataxia; and energy loss in the basal ganglia (along with thalamocortical hypometabolism) would result in paroxysmal movement disorders, such as dystonia, chorea, or tremors (Pons et al. 2015, Akman et al. 2015).

Current management of Glut1 DS consists of the ketogenic diet (KD) which has been shown to be effective in controlling seizures associated with Glut1 DS (Pong et al. 2012, Pearson et al. 2013). However, there is less evidence supporting the effects of KD on movement disorders experienced by Glut1 DS patients and a there is a continued effort to understand any potential effect that KD may have on these symptoms.

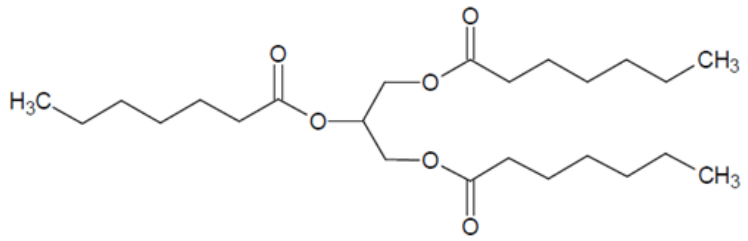
5.2 Brief Overview of UX007 Development

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:

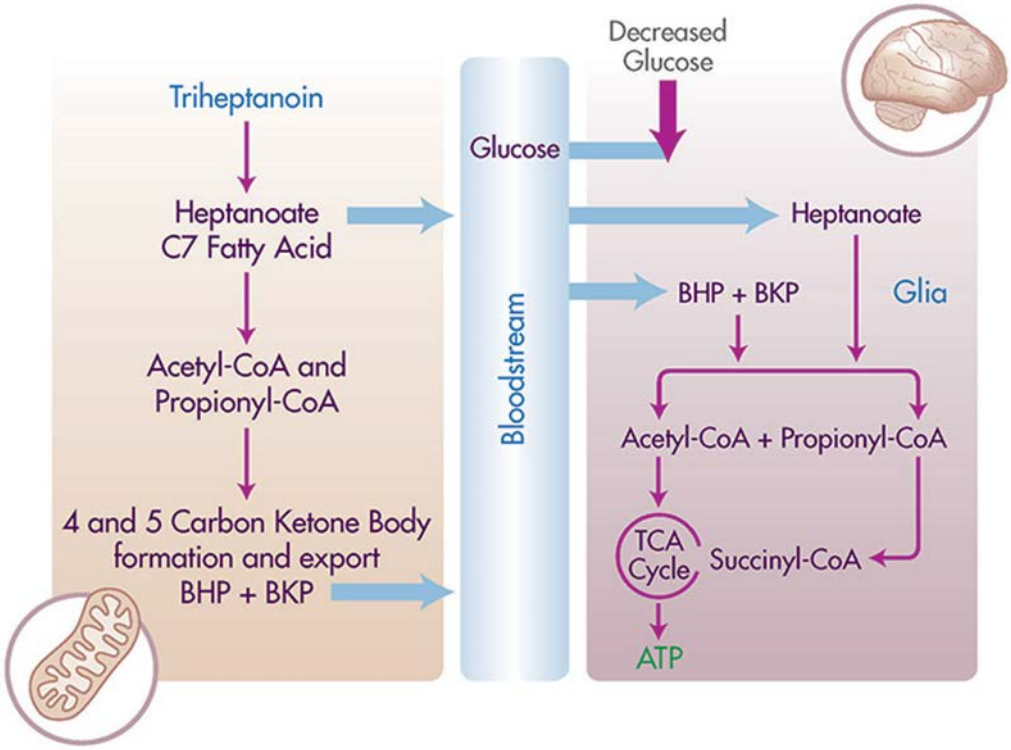


UX007 (triheptanoin) is a liquid, intended for oral (PO) administration. One thousand grams (1025 ± 25 g) of neat triheptanoin drug substance is filled into 1 liter (L), high density polyethylene (HDPE) or round, amber-colored glass bottles. UX007 is manufactured, packaged, and labeled according to Good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

5.2.1.1 Mechanism of Action in Glut1 DS

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

Figure 5.2.1.1.1: Proposed mechanism of UX007 action in Glut1 DS



5.2.2 Nonclinical Studies

Nonclinical studies evaluating triheptanoin and its metabolites in mice and rats have been published and further support the safety of UX007. These studies provide data on the absorption, metabolism, and toxicity of triheptanoin when administered intravenously and PO at doses up to 40% the recommended caloric intake. Furthermore, triheptanoin has been found to be effective in 4 animal models of epilepsy, similar to that of other AEDs (Borges et al. 2012, Willis et al. 2010, Thomas et al. 2012, Kim et al. 2013). Studies of potential clinical significance and relevance to this protocol are summarized below; additional details are provided in the IB.

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

Three non-GLP toxicology studies have been conducted: one acute study in rats at doses up to 5 ml/kg (CL74-95-1045), one 9 month toxicity study in rats at doses up to 1.14 g/kg/day (Ataide et al. 2009); a rat 9-month chronic study), and one dermal sensitization study in guinea pigs (CL74-95-1045). There were no systemic toxic effects in any study, although

hepatic steatosis was observed in all groups, including control animals, in the 9-month study. This is likely due to the high fat content in the diet and easier diffusion absorption of medium chain fat without bile (rats have no gall bladder), which is generally much less well tolerated in rat compared to human. Microscopic changes were observed in the intestinal cells but this effect was seen in all groups including controls. The dermal sensitization study indicated that triheptanoin is not a dermal sensitizer.

A Good Laboratory Practice (GLP) 9-month study in juvenile Yucatan minipigs was performed to further evaluate the toxicity and toxicokinetic (TK) profile of UX007 and five metabolites, including the C7 fatty acid heptanoic acid, two C5 ketone bodies (3-hydroxyvaleric acid and 3-ketovaleric acid), and two C4 ketone bodies (acetoacetic acid and beta hydroxyl butyric acid). There was no evidence of triheptanoin accumulation in plasma after daily dosing in feed at doses as high as 50% of daily caloric intake. Systemic exposure to triheptanoin and its metabolites was evident from the dose-related increase in plasma levels; there was no evidence of accumulation in plasma of triheptanoin and the metabolites after daily dosing for 9 months. No adverse treatment-related clinical signs were noted in any of the minipigs during the study and no treatment-related deaths occurred. No obvious treatment-related differences in body weight, body weight gain, hematology profiles, organ weights or diagnostic pathology were seen in minipigs receiving UX007 at 10, 30 or 50% of the caloric intake after 9-months of treatment. Alterations in clinical pathology (serum chemistry and hematology) profiles were considered secondary to the diet of the treated animals being lower in protein, iron and/or other nutrients. UX007 was well-tolerated at up to 50% of daily caloric intake and did not result in any evidence of systemic toxicity. As such, the 50% caloric replacement was considered the no-observed-adverse-effect level (NOAEL) for UX007 following 9-months of treatment.

A standard battery of genotoxicity tests was performed with UX007, including a Bacterial Reverse Mutation Test in *Salmonella typhimurium* and *Escherichia* (Ames), an In Vitro Mammalian Chromosome Aberration Test in human peripheral blood lymphocytes (Chromosomal Aberration), and a Mammalian Erythrocyte Micronucleus Test in rat bone marrow (Rat Micronucleus). UX007 was negative in all of these assays.

Developmental and Reproductive Toxicology (DART) GLP studies have also been conducted. The fertility study (Seg I) in rats did not reveal any impact on male or female fertility assessments. Furthermore, the embryo-fetal development (EFD; Seg II) studies in rats and rabbits did not reveal any impact on development of the fetus after exposure to UX007 during pregnancy.

5.2.3 Previous Clinical Studies

Clinical Studies in Glut1 DS Patients with Movement Disorders

In a recent, open-label Phase 2 study, paroxysmal manifestations improved significantly (p=0.028) in six evaluable patients, in response to treatment with triheptanoin (Mochel et al. 2015). In the study, subjects were asked to record all paroxysmal manifestations including motor (epileptic and non-epileptic) and non-motor (e.g. fatigue, headache, sleep disturbance, disorientation, and mood disorder) events prior to and post treatment with triheptanoin. The numbers of motor and non-motor events were reduced during treatment with triheptanoin followed by an increase in these paroxysmal events when triheptanoin treatment was subsequently withdrawn. Subjects were also asked to score changes in their clinical condition since the start of triheptanoin therapy. Patient-reported clinical global impression of improvement (CGI-I) scores demonstrated a clear improvement after the triheptanoin treatment period followed by worsening of their condition on withdrawal of treatment, tracking the temporal profile of changes in frequency of paroxysmal manifestations. Physicians also rated the severity of the study subjects based on their clinical experience with Glut1 DS and considered these subjects, in whom paroxysmal events were the primary manifestation of the disease, to be moderately to markedly ill. The most common motor manifestations included muscle stiffness, movement disorder, and weakness. All of these symptoms decreased in frequency when treatment with triheptanoin was initiated.

Studies in Glut1 DS Patients with Other Clinical Manifestations and Other Indications

More than 450 patients with various metabolic disorders of energy deficiency including Glut1 DS, have been treated with triheptanoin for periods up to 16 years with evidence of clinical benefit and no significant safety issues reported. In addition, over 100 patients with various metabolic disorders from our sponsored studies and expanded access and Investigator initiated studies, have been treated with UX007 with evidence of clinical benefit and no significant safety issues reported. These data support the safety of triheptanoin when administered at the proposed weight-based clinical dose range in adults and pediatric patients as young as neonates.

Triheptanoin has been studied for over a decade in a large cohort of patients with fatty-acid oxidation disorders (FAOD) as part of a compassionate use program (Roe et al. 2002, Roe et al. 2006, Roe et al. 2008, Barone et al. 2012). Ultragenyx is currently developing UX007 as a substrate replacement therapy for long-chain FAOD (LC-FAOD).

Patients with other disorders have also been treated with triheptanoin, including those with pyruvate carboxylase deficiency (Mochel et al. 2005), Huntington's disease (Mochel et al. 2010), adult polyglucosan body disease (APBD) (Roe et al. 2010), glycogen storage disease type II (GSD-II; Pompe disease) (Roe et al. 2006) and congestive heart failure (IND 65827). Triheptanoin treatment has been generally safe and well tolerated in subjects with these disorders.

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

Current Studies Sponsored by Ultragenyx

The Phase 2 randomized, double-blind, placebo-controlled study to assess the safety and efficacy of UX007 in pediatric, adolescent, and adult Glut1 DS patients experiencing seizures has recently completed study conduct (UX007G-CL201, data analysis ongoing). In addition, a prospective open-label Phase 2 study to assess safety and clinical effects of UX007 in subjects with LC-FAOD (UX007-CL201) is completed. Both studies have extensions into which subjects could enroll once they completed participation in the parent study (UX007G-CL202 and UX007-CL202, respectively).

The IB provides additional information on UX007 effects in humans and associated Reference Safety Information.

5.3 Summary of Overall Risks and Potential Benefits

UX007 is intended as a substrate replacement therapy to improve metabolism in patients with Glut1 DS. UX007 is being developed to address the needs of Glut1 DS patients who have paroxysmal movement disorder events. There exists a significant unmet medical need in these patients.

Over 450 patients with Glut1 DS and LC-FAOD or other diseases of energy metabolism have been treated with UX007 as part of clinical trials or expanded access (compassionate use) programs. Of these, >50 subjects were pediatric subjects with some as young as neonates; 23 received over 5 years treatment with triheptanoin. These data support the safety of triheptanoin when administered in pediatric patients as young as neonates.

Nonclinical studies evaluating triheptanoin and its metabolites in mice and rats have been published and further support the safety of triheptanoin in the Glut1 DS population. Data from the animal pharmacokinetic (PK), TK, and toxicity studies indicate that triheptanoin is well absorbed after oral dosing and is well-tolerated without overt toxicities at doses as high as 1.14 g/kg in mice and 50% daily caloric intake in juvenile minipigs for 9 months, with no signs of hepatic or renal injury.

Data from nonclinical and clinical studies to date suggest triheptanoin does not pose any serious safety risks that can be identified at this time. Triheptanoin has had no significant safety issues in humans and no toxicology or adverse pharmacology findings were 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). Commonly reported adverse effects are gastrointestinal distress and excessive weight gain at high doses. Both of these issues appear to resolve when triheptanoin is consumed in small doses mixed with foods throughout the day and when total caloric intake is appropriately managed. The current overall risk-benefit ratio of UX007 supports further clinical development for the treatment of Glut1 DS.

5.4 Study Rationale

Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS) is a rare, severely debilitating disease characterized by seizures, developmental delay, and movement disorders. 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 cerebral energy deficiency. Current management of Glut1 DS consists of the ketogenic diet (KD) which has been shown to be effective in controlling seizures associated with Glut1 DS (Pong et al. 2012, Pearson et al. 2013). However, there is less evidence supporting the effects of KD on movement disorders experienced by Glut1 DS patients.

The proposed mechanism for both paroxysmal motor and non-motor manifestations appear to be related to an energy deficit in the basal ganglia related to energy expenditure (Weber et al. 2008, Wang et al. 2012). These symptoms may be relieved to some extent by the KD, which also suggests an energy-dependent mechanism of action.

There are currently no approved therapies for the movement disorder events associated with Glut1 DS. Triheptanoin, a triglyceride composed of three heptanoate (C7 fatty acid) esters, 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. The proposed Phase 3 study is designed to assess the efficacy and safety of UX007 (triheptanoin) in reducing the frequency of episodic movement disorder events in Glut1 DS patients. This study will assess patients who are not currently treated with the ketogenic diet (KD), as this diet may affect some energy-dependent symptoms in Glut1 DS.

6 STUDY OBJECTIVES

The primary objective of the study is to:

- Evaluate the efficacy and safety of UX007 in the treatment of disabling paroxysmal movement disorders associated with Glut1 DS

6.1 Study Endpoints

Endpoints will be evaluated for UX007 and placebo treatment.

6.1.1 Primary Endpoint

The primary endpoint is the frequency of disabling paroxysmal movement disorders captured as movement disorder events observed during the Maintenance Period of treatment, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary.

6.1.2 Secondary Endpoints

- Duration of disabling paroxysmal movement disorder events observed during Maintenance Period of treatment, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary
- Walking capacity and endurance, as determined by the distance walked in 12 minutes in the 12 Minute Walking Test
- Patient/caregiver global impression of change in clinical status using the Clinical Global Impression – Improvement (CGI-I)
- Health-related quality of life assessing physical function, mobility, upper extremity function, fatigue, pain and social health using a PROMIS®-based questionnaire
- Cognitive function as measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB) (assessed at select sites)

6.1.3 Exploratory Endpoints

- Self-care, productivity, and leisure performance assessed by the Canadian Occupational Performance Measure (COPM)
- Physician global impression of change in clinical status using the Clinical Global Impression – Severity scale (CGI-S) and Clinical Global Impression – Improvement (CGI-I)
- Activity levels as measured by a wrist-worn actigraphy device at select study sites, where feasible. Endpoints include mean daytime activity, mean nighttime activity, and percent time in moderate or higher intensity activity

- Frequency and duration of disabling paroxysmal movement disorder events over time throughout the three year open-label Extension Period
- PK data for UX007 metabolites

6.1.4 Safety Endpoints

- Adverse events, including the subject incidence of adverse events (AEs), treatment related AEs, serious adverse events (SAEs), AEs leading to discontinuation and fatal AEs.
- Clinically significant changes in vital signs, clinical laboratory test results, and electrocardiogram (ECG)
- Change in suicidal ideation & behavior assessment as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

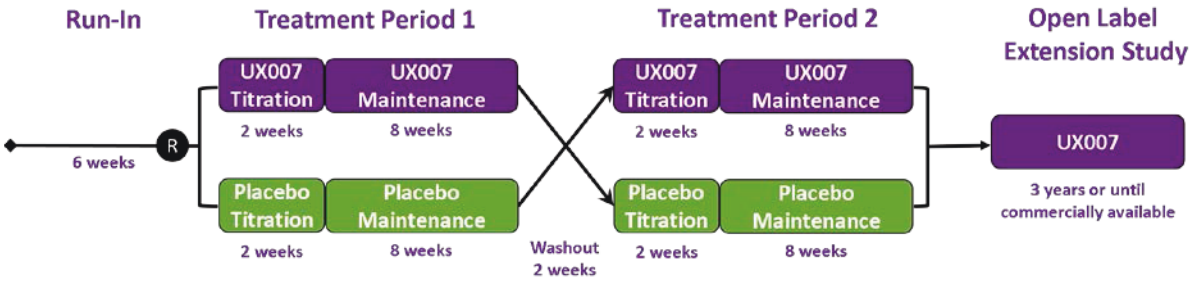
UX007G-CL301 is a randomized, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of UX007 in Glut1 DS. The study will enroll approximately 40 pediatric, adolescent, and adult subjects who are not on KD and are having disabling paroxysmal movement disorder events. In this study, movement disorder events are defined as disabling if they affect or limit a subject's physical functioning and activities of daily living such as caring for oneself, performing manual tasks, walking, standing, lifting things, bending, eating/swallowing, speaking, seeing, sleeping, attending or participating in school/work, or doing sports/exercise.

During the 6-week Run-in Period, subjects will record disabling paroxysmal movement disorder events in a daily electronic Glut1 DS symptom diary; if the minimum criterion for number of events is not met (or subjects complete <80% of the daily electronic Glut1 DS symptom diary), the subject will be considered a screen failure and will not be randomized. Individuals may be allowed to rescreen, at the discretion of the Principal Investigator, subject to approval by the Medical Monitor. At the discretion of the Sponsor and Principal Investigator, the Run-In Period may be extended beyond 6 weeks.

At the end of the Run-in Period, eligible subjects will be randomized (1:1 ratio) to one of two treatment sequences (UX007/placebo or placebo/UX007). At Randomization, subjects will begin a 10-week double-blind Treatment Period 1. At the end of Treatment Period 1, subjects will discontinue treatment and begin a 2-week washout period to minimize any potential carryover effect. Subjects will crossover to the second randomized, double-blind treatment assignment (placebo to UX007, UX007 to placebo) for an additional 10 weeks during Treatment Period 2. At the end of the blinded crossover period (Week 22), all subjects will have the option of rolling into the open-label Extension Period, to continue UX007 treatment for up to 3 years or until approval. Long-term safety and maintenance of effect of UX007 will be assessed during the open-label Extension Period. A Safety Follow-up Phone Call will be conducted 30-35 days after the last dose of UX007G-CL301 study drug. Figure 7.1.1 provides a schematic of the study design.

Dosing will be initiated in both Treatment Periods using a 2-week titration schedule until the subject has reached their age-related target dose (Table 7.4.4.1). If a subject has not reached the target dose by the end of the 2-week Titration Period, dose titration should continue until the maximum tolerated dose is reached. The age-related target dose of UX007 will be administered PO mixed thoroughly into food or drink (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 young children, decreasing to 1-2 g/kg for older children, adolescents, and adults.

Figure 7.1.1: UX007G-CL301 Study Schematic



7.2 Discussion of Study Design, Including Choice of Control Group

The choice of study design is based on the heterogeneity of the population to be studied. The impairment of glucose transport into the brain in Glut1 DS results in an energy deficit in various brain regions, including the cortex, basal ganglia and cerebellum. Damage to these brain regions may result in chronic deficits, such as cognitive delay, spasticity, ataxia or dystonic posturing (Gras et al. 2014). Against this background of neurologic impairment, the patient may also have acute periods of additional impairment, such as seizures, movement disorders or worsening ataxia (Pons et al. 2010). Some patients, especially those described as 'non-classical' may have minimal cognitive impairment, never have seizures, and present in their teens or later as a subset of a group of disorders called Paroxysmal Dyskinesias (Leen et al. 2010).

The variability in the types, frequency and severity of the paroxysmal movement disorders in Glut1 DS, a crossover study design was chosen because it will allow comparison of the responses of the same heterogeneous group to both treatment and placebo.

Although the ketogenic diet (KD) is often used as a treatment for seizures in Glut1 DS (Klepper et al. 2007), its use in treating Glut1 DS movement disorders is less well-established (Pons et al. 2010). The KD may be viewed as a burden for families and is often difficult to maintain as children reach adolescence, even when it has been effective in seizure control earlier in life. Many patients with movement disorders, such as Paroxysmal Dyskinesia, never had seizures and may never have been treated with KD. Implementation of the KD would be extremely difficult in a population that is likely to be older, seizure-free, and under less parental control than the younger population in whom seizures are a prominent feature.

In a Phase 2 study, paroxysmal manifestations improved significantly (p=0.028) in 6 evaluable patients, in response to treatment with triheptanoin (Mochel et al. 2015). The proposed Phase 3 study is designed to assess the efficacy and safety of UX007 (triheptanoin) in reducing the frequency of disabling paroxysmal movement disorder events in Glut1 DS patients who are not on KD.

7.3 Selection of Study Population

The study will be conducted in pediatric, adolescent, and adult Glut1 DS patients (aged ≥ 6 years). The age range of ≥ 6 years old was selected for this Phase 3 study because this age is consistent with the presentation of movement disorders and paroxysmal exertional dyskinesia associated with Glut1 DS (Alter et al. 2014), and is an appropriate patient population to accurately capture these manifestations with an event based daily Glut1 DS symptom diary.

Enrollment may include subjects from countries other than those with active sites; enrollment under these circumstances will be at the discretion of the Sponsor. 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, as will subjects with a BHB level greater than 1 mmol/L. There is less evidence supporting the effects of KD on movement disorders experienced by Glut1 DS patients and there is a continued effort to understand any potential effect that KD may have on these symptoms. Nevertheless, KD is prescribed in many 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.

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 will take all reasonable measures to ensure the protection and safety of this population by complying with all local or regional laws and regulations. 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.

The energy impairment in Glut1 DS produces variable manifestations according to the area of the brain most affected, but also due to other factors, such as severity of the *SLC2A1* mutation, nutritional status, patient activity level and emotional state (Pons et al. 2010, Gras et al. 2014); this results in a wide variety of phenotypes and clinical manifestations. The clinical presentation also tends to evolve as the patient becomes older. It has been noted that seizures are more prominent in early life, with movement disorders becoming more evident in late childhood and early adolescence (Alter et al. 2014, Gras et al. 2014).

Seizure types in Glut1 DS are variable and may include Generalized Tonic-Clonic, Partial Complex, Myoclonic, Focal and Absence (Mullen et al. 2010, Leen et al. 2010). Movement disorders due to Glut1 DS may also be variable, not only from patient to patient but within the same patient, probably due to factors involving lack of brain energy. Some patients may have movement disorders as a relatively chronic part of the clinical presentation; moderate ataxia or mild dystonic posturing of the hand when walking, for example. These findings may become more pronounced at times, possibly provoked by factors such as a fasting, fatigue or exercise (Pons et al. 2010). In addition, patients with relatively normal baseline neurologic status may also experience episodic movements

including dystonic posturing of one or more extremities, myoclonic jerks, or choreic movements. Some of this latter group may have been diagnosed with Paroxysmal Dyskinesias and may have minimal or no other symptoms of Glut1 DS. The movements in this subset of patients are frequently provoked by exercise (Erro et al. 2014).

Patients experiencing all types of disabling paroxysmal movement disorders from Glut1 DS will be included in 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, aged ≥6 years old at the time of informed consent
3. At least 8 disabling paroxysmal movement disorder events in the 12 weeks prior to Screening, by subject or caregiver report

   OR

   At least 6 disabling paroxysmal movement disorder events in any 6 consecutive week period, over the last 12 week period prior to Screening, by subject or caregiver report
4. At least 4 disabling paroxysmal movement disorder events in the first 6 weeks of the Run-in Period, reported in the daily electronic Glut1 DS symptom diary
5. ≥80% compliance with daily electronic Glut1 DS symptom diary completion during the Run-in Period
6. Not on KD, modified KD, or ketosis-inducing modified-fat diet for at least 3 months prior to Screening
7. Plasma level of beta-hydroxybutyrate (BHB) ≤ 1 mmol/L (non-fasting) at Screening
8. Provide written or verbal assent (if possible) and written informed consent by the patient (if an adult), or by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures
9. Must, in the opinion of the Investigator, be willing and able to complete key aspects of the study and be likely to complete the 22-week, placebo-controlled, Treatment Period
10. Patient (or caregiver) must, in the opinion of the Investigator, be able to comply with accurate completion of the study daily Glut1 DS symptom diary
11. Females of child-bearing potential must have a negative urine pregnancy test at Screening and Baseline and be willing to have additional pregnancy tests during the study. Females considered not to be of childbearing potential include those who have not experienced menarche, are post-menopausal (defined as having no menses for at least 12 months without an alternative medical cause) or are permanently sterile due to total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

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

7.3.2 Exclusion Criteria

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

1. Any known hypersensitivity to triheptanoin or safflower oil that, in the judgment of the Investigator, places the subject at increased risk for adverse effects
2. Prior use of triheptanoin within 30 days prior to Screening
3. History of, or current suicidal ideation, behavior and/or attempts per C-CSSRS at Screening or Baseline
4. Pregnant and/or breastfeeding an infant at Screening or Baseline
5. Participants unwilling or unable to discontinue use of a prohibited medication or other substance that may confound study objectives (Section 7.4.6.1 [MCT oil, barbiturates, pancreatic lipase inhibitors, KetoCal or other KD supplements, and/or KD])
6. Glut1 DS treatment regimen, including AEDs, should be stable for at least 30 days prior to Screening
7. Use of any investigational product (drug, medical food, or supplement, including medium chain triglyceride [MCT] oil, including coconut oil) within 30 days prior to Screening
8. 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
9. Feeding or nutrition that, in the opinion of the dietitian, potentially affects consistent administration of study drug

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:

- An illness or AE that, in the judgment of the Investigator or Ultragenyx, might place the subject at risk or affect study conduct (Section 8.5.4)
- Pregnancy of the subject or partner of a subject

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

- Initiation of KD or similar diet resulting in a BHB > 1 mmol/L
- Use of prohibited medications
- At the request of the subject (withdraws consent), Investigator, or Ultragenyx, for administrative or other reasons
- Protocol deviation or noncompliance

If a subject discontinues from the study prior to End of Treatment 2, every reasonable effort should be made to perform the Early Termination Visit procedures as soon as possible after the last dose of investigational product, and at most, within four weeks of discontinuation. Subjects who withdraw or are removed from the study after receiving study drug may be replaced on a case-by-case basis, at the discretion of Ultragenyx.

7.3.3.1 Stopping Rules

A Data Monitoring Committee (DMC) will be constituted for Study UX007G-CL301 and will act in an advisory capacity to monitor the safety of study subjects on a routine basis throughout the trial (Section 7.6.6). The DMC may provide advice to Ultragenyx in any determination of whether study enrollment should be paused or if the study should be stopped.

Individual subjects who experience an unexpected and possibly, probably, or definitely drug-related SAE (Section 8.5.3) that represents a change in the nature or an increase in frequency of the serious event from their prior medical history will be evaluated 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

At the Week 0 (Baseline 1) and at Weeks 12 (Baseline 2), 22, 34, 58, 82, 106, 130, and 154, subjects will be dispensed an adequate supply of study drug per their weight-based target total daily dose. Beginning at Week 22, all subjects will be dispensed UX007 for the open-label Extension Period. Due to the extended time between scheduled clinic visits, additional supplies of study drug may be shipped directly to the subject or a designated pharmacy for logistical purposes, per country regulations and upon Sponsor approval.

7.4.1 Investigational Product

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

The total daily dose will be divided into 4 equal doses, mixed with food or drink (or formula, as appropriate), and administered PO or by gastronomy tube at breakfast, lunch, dinner, and before bed. The dose may be divided into smaller more frequent doses with food or drink as needed. The oil should not be taken without mixing thoroughly with food or drink.

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 via an Interactive Web Randomization System (IWRS) based on a randomization schedule developed by an independent third-party vendor to maintain blinding.

7.4.4 Selection of Doses

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

UX007 (triheptanoin) is a liquid, intended for oral (PO) administration. UX007 is a colorless to yellow oil supplied in 1 L round, translucent high-density polyethylene (HDPE) or 1 L round amber colored glass bottles. Subjects will be dosed according to an age- and weight-based strategy (Table 7.4.4.1), up to a maximum daily administration of 130g. For subjects within 25% predicted BMI, actual body weight will be used to calculate the appropriate dose per the subject's age category. Adjusted body weight will be used for subjects with greater than 25% predicted BMI, to account for metabolic activity found in adipose tissue versus lean muscle. Adjusted body weight will be calculated in kilograms, using the following formula:

Formula 1# Adjusted Body Weight = Ideal Body Weight + [25% × (Actual Body Weight − Ideal Body Weight)]

UX007 dosing will be initiated using a 2-week titration schedule until the subject has reached his/her target total daily dose. If a subject has not reached the target total daily dose by the end of the 2-week titration period, dose titration should continue until the maximum tolerated dose is reached. For detailed information regarding dosing and titration, please refer to the Study Reference Manual.

Table 7.4.4.1: Age- based UX007 Target Total Daily Dose

Age Ranges	UX007 dose (g/kg/day) that is estimated equivalent to 30% total caloric intake
6 - 9 Years	2.5
10 - 14 years	2
15 - 20 years	1.5
21 and Over	1.2

The total daily dose will be divided into 4 equal doses, mixed with food or drink (or formula, as appropriate), and administered PO or by gastronomy tube at breakfast, lunch, dinner, and before bed. The dose may be divided into smaller more frequent doses with food or drink as needed. The oil should not be taken without thoroughly mixing with food or drink. The dose should not be adjusted due to changes in age and/or weight during Treatment Periods 1 and 2.

The data support the safety of triheptanoin when administered at approximately 1-4 g/kg depending on age. Previous clinical data also suggest an age-dependent dose that relates to the relatively higher energy requirements for young children versus older children versus adults. The 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, adolescents, and adults. 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.

7.4.4.1 Study Duration

Subject participation during the double-blind treatment period (including the Run-in Period, Baseline, Treatment Period 1, Washout, and Treatment Period 2) will be 28 weeks in duration; the Extension Period allows patients to receive UX007 for up to 3 additional years, or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, the study is terminated, or until commercial availability of the study drug in the subject's region, which occurs first. The total treatment duration enables a long-term assessment of the efficacy and safety of UX007 in Glut1 DS subjects with movement disorders. A Safety Follow-up Phone Call will be conducted 30-35 days after the last dose of UX007G-CL301study drug. The last subject's Safety Follow-up Phone Call is the defined End-of-Study Time Point.

7.4.5 Blinding

The Titration and Maintenance Periods (Weeks 0-22) will be conducted as a randomized, double-blind, placebo-controlled, crossover study. Double-blind conditions will be established during this period so that neither the sponsor, subject, or site personnel involved in study conduct will know the identity of a subject's treatment. After all subjects have completed the double-blind period, unblinding of the study will occur. All subjects who complete the double-blind portion of the study will be eligible to receive open-label UX007 during the Extension Period 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 an IWRS
- 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 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 before unblinding, when possible, but priority should be given to the safety of the subject.

Individual subject treatment assignment may be unblinded by the sponsor to satisfy expedited reporting requirements of regulatory authorities. The system to unblind treatment assignment will be maintained and executed through an IWRS which will be available 24 hours a day, 7 days a week.

If a subject's treatment assignment is unblinded prior to completion of the double-blind portion of the study, the subject may be discontinued from the study and may not be eligible to participate in 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, including coconut oil
- KetoCal or other KD supplements and medical foods containing MCT oil
- Barbiturates
- Pancreatic lipase inhibitors (e.g. Orlistat) due to possible inhibition of metabolism of tripheptanoin.

In the event of an emergency, any medication deemed necessary by the treating physician should be used as needed.

7.4.6.2 Permitted Medications

Other than the medications specifically prohibited in this protocol (Section 7.4.6.1), subjects may receive concomitant medications as required. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during 30 days prior to Screening will be reviewed and recorded in the CRF. The Glut1 DS treatment regimen, including AEDs, should be stable for at least 30 days prior to Screening, and for the duration of the double-blind treatment period through Week 22.

7.4.7 Treatment Compliance

At the Week 0 (Baseline Period 1) and at Weeks 12, 22, 34, 58, 82, 106, 130, and 154, subjects will be dispensed an adequate supply of study drug per their weight-based target total daily dose. Due to the extended time between scheduled clinic visits, additional supplies of study drug may be shipped directly to the subject or a designated pharmacy for logistical purposes, per country regulations and upon Sponsor approval. Subjects and/or caregivers will use a study medication diary to record daily consumption of study drug. Subjects will be instructed to return all used (empty study drug containers) study drug to the site at the next visit. Site personnel will maintain a record of all medication dispensed to each subject and returned to the site. Over the course of the study for each subject, each bottle dispensed must be accounted for (returned to the site empty, partial, or full), and reconciled to the consumption reported in the daily Study Medication diary. Metabolite levels may also be used as supportive measures of treatment compliance (Section 7.5.3). Refer to the Pharmacy Manual for additional information on study drug accountability.

7.5 Study Procedures and Assessments

Whenever possible, study site staff (including trained clinicians, dietitians, physical therapists, and the Investigator or site designee) performing the assessments should be consistent from visit to visit throughout the 22-week double blind period. The parameters to be assessed, along with timing of assessments, are provided in the Schedule of Events (Table 2.2 and Table 2.3). Refer to the Study Reference Manual for additional details on specific assessments and the suggested order of administration.

The effects on Glut1 DS clinical features will be studied over the blinded Treatment and Open-label Extension Periods of the study.

7.5.1 Visit Schedule

Informed consent must be obtained prior to any Screening procedures. Subjects will return to the clinic at Baseline (Week 0), Weeks 10, 12, and 22 during the double-blind crossover portion of the study; and at Weeks 34, 58, 82, 106, 130, 154, and 178 during the extension period (Table 2.2 and Table 2.3). For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination visit procedures as soon as possible after the last dose of investigational product, or at least within 4 weeks of discontinuation. Telephone visits will occur at Weeks 2, 4, 6, 14, 16 & 18 during the double-blind crossover portion of the study and at Weeks 26, 30, 46, 70, 94, 118, and 142 during the Extension Period, where information related to adverse event and concomitant medications, as well as Glut1 DS symptom and study medication diary reviews, dose titration, and compliance will occur. Unscheduled clinic visits or telephone calls may be arranged at the site's discretion to provide additional dietitian follow up and other study support. A Safety Follow-up Phone Call will be conducted 30-35 days after the last dose of UX007G-CL301 study drug. The site personnel will initiate this safety follow-up telephone call to collect information on any ongoing or new AEs, SAEs, and concomitant medications.

Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.

7.5.2 Efficacy Measures

The concept for evaluation is to study the effects of UX007 treatment of disabling movement disorder events 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 number of disabling paroxysmal movement disorder events observed during the Maintenance Period of Treatment Periods 1 and 2, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary. The effect of UX007 treatment on Glut1 DS will also be assessed by evaluating additional criteria impacting motor and neurological function, along with relevant biomarkers and metabolites. Secondary and exploratory efficacy endpoints related to the effects of UX007 will help to define whether UX007 has effects on movement disorders experienced by Glut1 DS patients. The efficacy measures and assessments are described below; planned analysis of efficacy endpoints is described in Section 7.6.3. If, in the judgement of the Investigator, a patient is not able to safely perform an assessment, it does not need to be conducted at that study visit. Refer to the Study Reference Manual for additional details on the efficacy measures.

7.5.2.1 Subject Daily Glut1 DS Symptom Diary: Paroxysmal Movement Disorders of Glut1 DS

An event-based, daily Glut1 DS symptom diary will allow the subject/caregiver to capture quantitative and qualitative aspects of disabling paroxysmal movement manifestations of Glut1 DS, including but not limited to, frequency, duration, impact, and symptom type. A movement disorder event is defined for this study as a period of time when the subject experiences one or more movement disorder symptoms, including symptoms that are experienced during a movement disorder event alone or significant worsening of continuous movement disorders. In this study, movement disorder events are defined as disabling if they affect or limit a subject's physical functioning and activities of daily living, and this definition closely aligns with the definitions of disability provided by the World Health Organization (WHO) and the Americans with Disabilities Act (ADA). Disabling movement disorder events will be characterized in the daily Glut1 DS symptom diary as those that affect/limit major life activities such as caring for oneself, performing manual tasks, walking, standing, lifting things, bending, eating/swallowing, speaking, seeing, sleeping, attending or participating in school/work, or doing sports/exercise. The daily Glut1 DS symptom diary has been developed for both self- and caregiver-reporting based on age and cognitive ability. Diary reporters, whether the subject or caregiver, must complete a diary training module at the Screening Visit; reporters must remain constant throughout the Run-in Period, Treatment Period 1, Washout Period, and Treatment Period 2 (Weeks -6 to 22). Respondents should maintain ≥80% compliance with daily Glut1 DS symptom diary completion during the Run-in Period, Treatment Period 1, Washout Period and Treatment Period 2.

7.5.2.2 Functional Outcome: 12 Minute Walk Test (12MWT)

The 12MWT is a variation of the 6MWT used to assess endurance through walking (McGavin et al. 1976, Cooper 1968). The 12MWT will be administered by a trained clinician in accordance with general principles set forth in the American Thoracic Society (ATS) guidelines (ATS 2002) established for the 6MWT. Subjects will be observed by trained study staff throughout the duration of the 12MWT, and the test will not be performed if there are any concerns as to whether the subjects can reliably and safely complete the 12MWT. Subjects who meet the safety criteria will be instructed to walk the length of a pre-measured 20 meter course in a hallway for 12 consecutive minutes. Traffic cones will be used to standardize the lap distance. The subject will walk laps around the cones until the time period has expired. Instructions and encouragement will be given according to the script provided in the ATS guidelines with accommodations made for young children to improve compliance and understanding. The distance walked at the end of 12 minutes will be recorded in meters. The distance walked after 6 minutes will also be recorded. The percent of predicted normal values will be calculated for the 6MWT distance using age appropriate reference data (Gibbons et al. 2001, Geiger et al. 2007). HR and BP will both be recorded before the 12MWT along with post-test HR. The test may be discontinued at any time at the discretion of the administering clinician if there are concerns about the occurrence of any major safety event, including the onset of dizziness, chest pain, muscle pain, and respiratory distress.

7.5.2.3 Clinical Status: Patient Global Impression of Severity and Improvement

Patient/caregiver global impression of change in clinical status will be assessed using the Clinical Global Impression - Severity scale (CGI-S) pretreatment and Clinical Global Impression - Improvement (CGI-I) post-treatment.

Patients will be asked to rate the severity of their overall condition at the start of the study using a 4-point Likert rating scale.

Patients will be asked to rate the change in their overall condition since the start of the study using a 7-point Likert rating scale.

7.5.2.4 Clinical Status: Physician Global Impression of Severity and Improvement

Physicians will rate disease severity at pretreatment (CGI-S) and continue to rate severity for the duration of the study. Physicians will also record the degree of change in clinical status (CGI-I) at post treatment visits.

Physicians will be asked to rate the severity of the subject's overall condition at the start of the study using a 4-point Likert rating scale.

Physicians will be asked to rate severity and change in the subject's overall condition since the start of the study using a 4- and 7-point Likert rating scale, respectively.

7.5.2.5 Health-Related Quality of Life: PROMIS® questionnaire

The Patient-Reported Outcomes Measurement Information System (PROMIS®) was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being (Broderick et al. 2013, NIH 2015). The PROMIS® contains a bank of questions from which relevant items have been extracted and used to create a questionnaire to measure physical function, mobility, upper extremity function, fatigue, pain and social health. The PROMIS® questionnaires have been developed for both self- and proxy-report based on age and cognitive ability. The version used at Baseline 1 (Week 0) will be administered throughout Treatment Periods 1 and 2. If a subject ages out of the pediatric version during the Extension Period, the adult questionnaire may be administered at the discretion of the PI and Medical Monitor.

7.5.2.6 Cognitive Function

Cambridge Neuropsychological Test Automated Battery (CANTAB): Neuropsychological function measured using a standardized, non-verbal, computerized battery of tests designed to assess cognitive domains relevant to Glut1 DS such as attention and memory.

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).
The CANTAB tests will be administered by a trained clinician at select sites in a standardized order to minimize variability.

7.5.2.7 Activity Levels

A wrist-worn activity monitor (actigraphy device) will assess the impact of Glut1 DS on activity at select study sites, where feasible. Endpoints (including mean daytime activity, mean night time activity, and percent time in moderate or higher intensity activity) will be measured during the last 10 days of the Run-in Period, the last 10 days of Treatment Period 1, and the last 10 days of Treatment Period 2.

7.5.2.8 Qualitative Assessment

The Canadian Occupational Performance Measure (COPM) was developed as an evidence-based patient-centered tool to enable individuals/caregivers to identify and prioritize everyday issues that restrict or impact their performance in everyday life (Law et al. 1990). The COPM will be used to assess performance areas of self-care, leisure, and productivity.

7.5.3 Drug Concentration Measurements and Bioassays

To assess the UX007 metabolites, blood samples will be collected at Baseline 1 and 2, End of Treatment 1 and 2, and at Week 34. Blood for plasma at Baseline Visits will be collected pre-dose (within 15 minutes). Blood for plasma at End of Treatment visits will be collected approximately 90 minutes post dose. At Week 34, subjects will be administered one of their 4 daily doses (preferably their 2nd dose of the day) in order to collect appropriately timed PK samples (i.e., pre-dose and at [± 5 minutes] 30, 90, and 120 minutes post-dose). For each sample collection, the time elapsed since last study drug administration will be recorded on the CRF. The following UX007 metabolites will be assessed:

- Beta-hydroxypentanoate (BHP): Baseline 1 and 2, End of Treatment 1 and 2, and Week 34 visit
- Beta-hydroxybutyrate (BHB):
  - To monitor UX007 metabolites at Baseline 1 and 2, End of Treatment 1 and 2, and Week 34
  - For Ketosis detection at Screening (to confirm that the subject is not in a state of ketosis upon entry to the study) and each subsequent clinic visit in the double-blind Treatment and Extension periods.
- Plasma heptanoate: Baseline 1 and 2; End of Treatment 1 and 2; Week 34; and may be assessed at other Extension visits at Sponsor discretion
- Plasma acylcarnitines: Baseline 1 and 2; End of Treatment 1 and 2; Week 34; and may be assessed at other Extension visits at Sponsor discretion

Refer to the Study Reference Manual for additional details.

7.5.4 Safety Measures & General Assessments

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

7.5.4.1 Medical History

Medical history will be obtained at the Screening Visit. General medical information includes subject demographics (date of birth, ethnicity, and sex) and a history of major medical illnesses, diagnoses, and surgeries. The review will also include an assessment of phenotypic characteristics associated with Glut1 DS, including seizures, cognitive impairment, movement disorders, and microcephaly. The specific history of Glut1 DS will be recorded, along with date of onset, clinical presentation, and date and method of confirmed diagnosis. Any available family history of Glut1 DS will be noted including diagnosis, disease course, treatment and outcome. Please refer to Section 7.5.4.9 for Concomitant Medications reporting instructions.

7.5.4.2 Vital Signs, Height, 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, temperature in degrees Celsius (°C), and head circumference (cm). Vital signs measurements will be performed at every clinic visit before any additional assessments are completed; clinically significant changes will be recorded as AEs.

Height (in centimeters), and weight (in kilograms) will be obtained using a scale.

7.5.4.3 Physical Examination

Complete physical examinations will be performed at Screening and focused physical examination will be completed at all subsequent clinic visits, including Early Termination. The complete physical examination will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, and musculoskeletal systems. Clinically significant changes will be recorded as AEs.

7.5.4.4 Neurological Examination

A neurological examination will be performed by a neurologist at Baseline 1 (Week 0) and subsequent clinic visits, including Early Termination. Neurological examinations must evaluate, at a minimum, the following domains: Cranial nerves II-XII, motor function (dexterity, tone, and strength), sensory, cerebellar, gait, and deep tendon reflexes. Changes in the neurological exam will be recorded, and the emergence of clinically significant abnormalities will be reported as AEs.

7.5.4.5 Clinical Laboratory Tests

The clinical laboratory evaluations to be performed in this study include routine serum chemistry, lipid profile (in adults aged 18 or older), hematology, urinalysis, and ketosis detection; specific analytes are listed in Table 7.5.4.5.1. Clinical laboratory testing will be performed at each scheduled clinic visit (or Early Termination visit) and analyzed by a central laboratory. Blood and urine samples will be collected. Overnight fasting (8-12 hours)

is required prior to lipid profile tests at Baseline 1 (Week 0), End of Treatment 1 (Week 10) and End of Treatment 2 (Week 22) as well as every 24 weeks during the Extension Period (Weeks 34, 58, 82, 106, 130, 154, and 178 or Early Termination Visit). Lipid profile evaluations will be performed only in adults (aged 18 or older). Fasting is not required for clinical laboratory tests in subjects < 18 years old or in subjects ≥ 18 years old prior to clinical visits when lipid profile assessments are not being performed (Screening or Baseline Visit 2). Clinically significant changes will be recorded as AEs. Refer to the Study Reference Manual for additional details.

Table 7.5.4.5.1: Clinical Laboratory Assessments

Chemistry	Hematology	Urinalysis	Ketosis Detection	Lipid Profile
Alanine aminotransferase (ALT)	Hematocrit	Appearance	Beta-hydroxybutyrate (BHB)	Low-density lipoprotein (LDL)
Alkaline phosphatase	Hemoglobin	Color		High-density lipoprotein (HDL)
Aspartate aminotransferase (AST)	Platelet count	pH		Triglycerides
Bilirubin (total)	Red blood cell (RBC) count	Specific gravity		Total cholesterol
Blood urea nitrogen (BUN)	White blood cell (WBC) count	Ketones		
Calcium		Protein		
Chloride		Glucose		
Serum creatinine		Pregnancy test (if applicable)		
Gamma-glutamyl transpeptidase (GGT)				
Serum glucose				
Potassium				
Protein (albumin and total)				
Sodium				
Creatine Kinase				

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

7.5.4.6 Electrocardiogram

A standard 12-lead ECG will be performed at a resting heart rate during the Baseline 1 visit (Week 0), End of Treatment 1 (Week 10), and End of Treatment 2 (Week 22), and every 48 weeks throughout the Extension Period (Weeks 58, 106, and 154 or Early Termination visit, if applicable). ECG will not be performed at the Early Termination visit if the assessment has been performed within 3 months of termination. ECG results will be read locally by qualified personnel. Abnormal findings and clinically significant changes from baseline will be recorded as AEs.

7.5.4.7 Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests at Screening and at all clinic visits (or Early Termination). Females considered not of childbearing potential include those who have not reached menarche, are post-menopausal (defined as having no menses for at least 12 months without an alternative medical cause), or are permanently sterile due to total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Female subjects with a positive pregnancy test at Screening or Baseline will not be enrolled in the study; Pregnancy in subject or partner must be reported (Section 8.5); pregnant subjects will be discontinued from the study. Additional pregnancy tests may be performed at any time in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result, or can be performed if pregnancy test by urine is not feasible.

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

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

7.5.4.8 Suicidal Ideation and Behavior Assessments

Assessment of suicidal ideation and behavior is a regular part of development programs involving AEDs and other neurologic drugs with central nervous system activity (FDA Draft Guidance 2012). The Columbia Suicide Severity Rating Scale (C-SSRS) is a standardized suicidal rating instrument used to assess the suicidal ideation and behavior in an at-risk population (Posner et al. 2011). To prospectively assess suicidal ideation and behavior, the C-SSRS will be administered by a clinician. Depending on the cognitive state of the subject, some questions within the C-SSRS may be deemed by the Investigator to be inappropriate to ask the subject and can be omitted. Suicidal ideation and behavior will be assessed in subjects who are ≥ 10 years of age at each visit. The *Baseline* questionnaire will be administered at Screening; 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.

7.5.4.9 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit, beginning at Screening. 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. Glut1 DS treatment history, including UX007 (triheptanoin) treatment history, and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen) during the 30 days prior to Screening, during the study, and 30 days following the last administration of study drug. 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 procedures and/or concomitant therapy, including physical/occupational therapy, will be recorded.

7.5.4.10 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 in vital signs, clinical laboratory, or ECG parameters will be recorded as AEs or SAEs, if appropriate, as well as any increases in frequency or severity or changes in type of Glut1 DS associated symptoms (including but not limited to seizures, movement disorders, behavioral abnormalities, cognitive function, etc.).

A blood sample will be collected for UX007 metabolite concentrations in the event of an SAE, if feasible.

7.5.4.11 Dietary Assessment and Consultation

A dietary consultation which includes nutrition assessment and training on completion of the 3-day diet diary will occur at Screening. Subjects and/or caregivers are required to maintain a record of the subject's 3-day diet diary for a consecutive 3-day period (representative of the subject's typical diet) approximately 7 days prior to the next clinic visit. The initial 3-day diet history obtained prior to the Baseline 1 Visit (along with plasma level of BHB ≤ 1 mmol/L at 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 diary will be reviewed by the site dietitian, or designee, at each applicable visit to the clinic so that the diet remains isocaloric and well-balanced. The dietitian, or designee, will also telephone subjects and/or caregivers at Weeks 0, 2, 4, 6, 10, 12, 14, 16, 18, and 22 to provide dietary advice and support and review of the study medication diary. Unscheduled clinic visits or telephone calls may be arranged at the site's discretion to provide additional dietitian follow up and other study support. Refer to the Study Reference Manual for details on the dietary assessment.

7.5.5 Appropriateness of Measures

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

A daily Glut1 DS symptom diary will be used by subjects and/or caregivers to capture disabling paroxysmal movement disorder events, completed on a daily basis, thereby minimizing recall bias. A 12 Minute Walk Test (12MWT) is included as a quantitative, objective measurement of endurance and walking capacity.

Physician- and patient/caregiver-reported outcomes are also included to assess health-related quality of life and activities of daily living including CGI severity and change scales. Health-related quality of life is further supported by the PROMIS® questionnaire which includes assessment of physical function, mobility, upper extremity function, fatigue, pain and social health. The CANTAB is included as a measure of cognitive function at select sites.

Because Glut1 DS symptoms including fatigue, energy deficiencies, and disabling dyskinesia events may limit a subject's ability to participate in everyday activities, activity levels may be assessed by a wrist-worn actigraphy device. A qualitative component will also be investigated with the Canadian Occupational Performance Measure (COPM) with a specific focus on the performance areas of self-care, leisure, and school/work productivity.

UX007 metabolites will be assessed using blood samples. The panel has been included to provide additional metabolite data on peak levels at steady-state. Where possible, timing of

assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary sampling.

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs and weight, ECG, serum chemistry, lipid profile, urinalysis and hematology, concomitant medications, and other routine clinical and laboratory procedures. For patients ≥10 years of age, suicidal ideation and behavior will be assessed at each clinic visit as an additional safety measure given the central nervous system involvement with Glut1 DS.

7.6 Statistical Methods and Determination of Sample Size

7.6.1 Determination of Sample Size

Based on the targeted patient population and eligibility criteria, it is estimated that during a 6 week duration, the subjects receiving placebo will have a mean frequency of 8 disabling paroxysmal movement disorders per 4 weeks, while subjects receiving UX007 will have a mean frequency of 4 disabling paroxysmal movement disorders per 4 weeks, and a standard deviation of the difference of 7.4. A total sample size of 40 subjects (20 subjects in each treatment sequence) will have at least 85% power to detect such difference between UX007 and placebo groups. This sample size assumption incorporates a projected discontinuation rate of 15%.

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 Planned Methods of Analysis

Analysis of Primary Endpoint

The primary analysis will compare the frequency of paroxysmal movement disorders captured as disabling movement disorder events (normalized to a 4 week rate) observed during the Maintenance Period of treatment with UX007 to the frequency of movement disorders captured as movement disorder events (normalized to a 4 week rate) observed during the Maintenance Period of treatment with placebo, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary.

The primary analysis will be performed using a weighted ANCOVA model, with study baseline frequency of movement disorder as a covariate, treatment sequence, treatment group and period as fixed effects, and a random effect for subject within the sequence.

When there is strong evidence suggesting that the normality assumption is not met, Wilcoxon rank-sum test will be considered as the primary analysis to assess the primary endpoint

Analyses of Secondary Endpoints

If the primary analysis for the primary efficacy endpoint is statistically significant, then a sequential testing strategy will be implemented for selected secondary efficacy endpoints in the following order:

- Duration of disabling paroxysmal movement disorder events analyzed by weighted ANCOVA model
- Change from baseline in 12MWT distance analyzed by ANCOVA model
- Patient/caregiver global impression of change in clinical status using the Clinical Global Impression – Improvement (CGI-I) analyzed by ANCOVA model

When there is strong evidence that the assumption is not met, Wilcoxon rank-sum test will be considered as the primary analysis to assess treatment difference.

- For the rest of the secondary endpoints, change from Baseline to the end of Maintenance Period in PROMIS domain scores and change from Baseline to the end of Maintenance Period in CANTAB scores will be analyzed by ANCOVA model.

Analyses of Exploratory Endpoints

ANCOVA model will be applied to analysis the following exploratory endpoints:

- Change from Baseline to the end of Maintenance Period in Canadian Occupational Performance Measure (COPM) scores
- Physician global impression of change in clinical status using the Clinical Global Impression – Severity scale (CGI-S) and Clinical Global Impression – Improvement (CGI-I)
- Change from study baseline in activity levels measured by a wrist-worn actigraphy device

7.6.3.1 General Principle

A general description of the statistical methods to be used to analyze the efficacy and safety of the study drug is outlined below. The analyses planned in this protocol will be expanded in the SAP to include detailed description of the analyses. The SAP will be finalized and approved prior to the database lock. Any deviations from the analyses described in the protocol and SAP will be noted in the final clinical study report.

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. In general, missing data will be treated as missing and no statistical imputation method will be used unless stated otherwise. The procedures for handling missing, unused, or spurious data, along with the detailed method for analyses, will be presented in the SAP.

Descriptive statistics will be used to summarize the data. For quantitative variables, the mean, standard deviation, median, quartile, minimum, and maximum will be provided. For categorical data, the frequency and percent distributions will be provided.

The number of subjects randomized, who complete each of the treatment periods, and discontinue the study will be summarized. Demographics (age, gender, race, ethnicity, and region) and other baseline disease characteristics will be summarized using descriptive statistics.

7.6.3.2 Efficacy Analysis

The primary endpoint will be analyzed based on the efficacy analysis set using a mixed-model ANCOVA model with fixed effects for treatment sequence, treatment group, period, and a random effect for subject within the sequence. The specific model will be defined in the SAP. The hypothesis that there is no difference in mean frequency of disabling paroxysmal movement disorder events per 4 weeks between treatment groups will be tested at the α=0.05 (2-sided) level.

For change-from-baseline efficacy endpoints, the baseline will be the last measurement taken prior to or on the first dose date of the first period for computation of the change from baseline value. The secondary efficacy endpoints will be analyzed using the same method as for the primary endpoint.

7.6.3.3 Safety Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class, Preferred Term (PT), relationship to study drug, and severity. All reported AEs with onset during the 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 study drug during the double-blind period, and also throughout the study including the open-label 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 will be used in the summary of laboratory data. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside of reference ranges) and/or

clinically significant abnormalities (as determined by the Investigator) will be presented for each clinical laboratory measurement. For C-SSRS, the percentage of subjects reporting any treatment emergent suicidal ideation and any treatment emergent suicidal behavior will be summarized descriptively by treatment group and visit week, respectively. The SAP will provide additional details on the planned safety analyses.

7.6.4 Pharmacokinetic and Bioassay Analyses

Descriptive statistics, including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for each plasma UX007 metabolite (BHB, BHP, acylcarnitine, and heptanoate) at each sampling time point to evaluate peak levels. Data will be listed for all subjects with available plasma concentrations. All concentrations below the lowest quantifiable concentration of the assay or missing data will be labeled as such in the concentration data listings. Concentrations below the lowest quantifiable concentration of the assay will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report. Results for each plasma UX007 metabolite will be provided.

7.6.5 Interim Analysis

No formal interim analysis is planned for this study.

7.6.6 Data Monitoring Committee

An independent DMC that includes members with expertise in movement disorders will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial. A review of blinded and unblinded safety data will be conducted by the DMC periodically. Ad hoc meetings will be held if indicated based on observed events. The roles and responsibilities of the DMC will be defined in the DMC Charter.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board or Ethics Committee and Competent Health Authority

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), if applicable, must be submitted to the Competent Health Authority and 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 Competent Health Authority and 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. Competent Health Authority and 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 Competent Health Authority and IRB/EC for review and approval.

8.1.2 Ethical Conduct of Study

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

8.1.3 Subject Information and Consent

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

It is the Investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of the study have been fully explained to each potential subject. The Investigator must explain to each subject that the subject is completely free to refuse to enter the study or to withdraw from it at any time. Subjects under the age of 18 years (or 16 years, depending on the region) will provide written assent (if possible), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects. Minors who reach legal age during the course of the study must provide written informed consent when eligible.

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

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

8.2 Investigators and Study Administrative Structure

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

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

A Coordinating Investigator will be identified for multicenter trials. The Coordinating Investigator will be selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator will read and sign the Clinical Study Report (CSR) in accordance with regulatory authority 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. 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. To ensure the subject is dispensed the correct amount of study drug and captured throughout Treatment Periods 1 and 2 as well as the Extension Visits, final titrated dose will be recorded in the IWRS. 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 uninterpretable data will be resolved in coordination with the Investigator.

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

The Investigator understands that regulatory authorities, the IRB/EC, and/or Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection. The Investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

8.4.3 Record Retention

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

8.5 Reporting and Follow-up of Adverse Events

8.5.1 Definition of Adverse Events

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

Suspected Adverse Reaction is any 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 adverse event or suspected adverse reaction that, in the view of either the Investigator or Sponsor, places the patient or subject at immediate risk of death. Life-threatening AEs do not include an AE or

suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event (SAE) or serious suspected adverse reaction is an adverse event or suspected adverse reaction that at any dose, in the view of either the Investigator or 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 disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect

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

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

8.5.2 Severity of Adverse Events

Wherever possible, the severity of all AEs will be graded using the NCI CTCAE (Version 4.03). 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", the following note of clarification is provided: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3 Relationship of Adverse Events to Study Drug

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

Categories of attributions for "Unrelated" events:

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

Categories of attributions for "Related" events:

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

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

8.5.4 Adverse Event Reporting

8.5.4.1 General

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

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

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

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

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

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

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

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

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

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

8.5.5 Communication Plan

8.5.5.1 Serious Adverse Drug Reaction Reporting

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

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

8.5.5.2 Urgent Safety Matters and Non-SUSAR Reporting

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

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

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

8.5.5.3 Pregnancy Reporting

Reported pregnancy of a subject or a subject's partner, while participating in the study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is known. Any pregnancy-associated SAEs will be reported as per the SUSAR reporting process indicated in Section 8.5.4.3.

8.5.5.4 Safety Contact Information

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

8.6 Financing and Insurance

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

8.7 Publication Policy

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

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10 SIGNATURE PAGE

Protocol Title: A Phase 3, randomized, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of UX007 in the treatment of movement disorders associated with Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

Protocol Number: UX007G-CL301 Amendment 3

I have read Protocol UX007G-CL301. 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

PPD

Melanie Brandabur, MD
Medical Director
Ultragenyx Pharmaceutical Inc.

Date