STATISTICAL ANALYSIS PLAN

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:	**UX007G-CL301**
Investigational Product:	**UX007 (Triheptanoin)**
Phase:	**3**
Sponsor:	**Ultragenyx Pharmaceutical Inc.** **60 Leveroni Court** **Novato, CA, USA 94949**
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Date:	**05 Sep 2018**
Version Number:	**2.0**

STATISTICAL ANALYSIS PLAN

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL301 Version 2.0

05 September 2018

The Statistical Analysis Plan for UX007G-CL301 (Version 1.0, dated 13 Dec 2017) has been amended with major changes summarized below.

1. Section 4.6 has been included to define subgroups for analysis. Section 8.8.1 and Appendix A include now the statistical methods for analyses of the subgroups defined in Section 4.6.

   Rationale: to examine the treatment effect in these subgroups.

2. Revised section 5.8 to define PROMIS final T scores from the PROMIS online scoring system.

   Rationale: PROMIS final T scores will be used for analysis as this is calibrated score based on a relevant reference population.

3. Added language in section 4.3 to have 12MWT, Patient/caregiver CGI-I, and CANTAB during OLE period as exploratory endpoint and added language in section 8.8.3 to specify corresponding analysis.

   Rationale: In Protocol Amendment 3, these assessments were added through the Extension Period for evaluation of long-term efficacy.

4. In section 3.1, added statement "At the discretion of the Sponsor and Principal Investigator, the Run-In Period may be extended beyond 6 weeks."

   Rationale: to be consistent with Protocol Amendment 3.

5. In section 8.9.3, add "head circumference" to vital sign assessment.

   Rational: to be consistent with Protocol Amendment 3.

6. Appendix B and C have been changed to follow Protocol Amendment 3

   Rational: to be consistent with Protocol Amendment 3.

7. In section 5.6 and section 7.3, modify the language for clarification.

   Rational: revised for clarification.

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ABBREVIATIONS

12MWT	12-Minute Walk Test
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
COPM	Canadian Occupational Performance Measure
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DB	Double-Blind
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration (United States)
Glut1	Glucose Transporter Type 1
Glut1 DS	Glucose Transporter Type 1 Deficiency Syndrome
IWRS	Interactive Web Randomization System
KD	Ketogenic Diet
MedDRA	Medical Dictionary for Regulatory Activities
MOT	Motor Screening Test
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLE	Open-Label Extension
PAL	Paired Associates Learning
PALFTMS	Paired Associates Learning First Trial Memory Score
PALTEA	Paired Associates Learning Total Errors (Adjusted)
PK	Pharmacokinetics
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

SI	Le Système International d'Unités (International System of Units)
SOC	System Organ Class
SSP	Spatial Span
SSPSLF	Spatial Span Length
SWM	Spatial Working Memory
SWMBE48	Spatial Working Memory Between Errors
SWMS68	Spatial Working Memory Strategy
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
UX007	Triheptanoin
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the UX007G-CL301 Protocol Amendment 3 dated 10July2018. This is the first amendment of SAP for this study. Changes from these guidelines must be substantiated by sound statistical reasoning and documented in the clinical study report (CSR).

The data collected in this study will evaluate the efficacy and safety of UX007 (triheptanoin) in the treatment of disabling paroxysmal movement disorders associated with Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS) compared to placebo. The primary efficacy endpoint for this study is the frequency of disabling paroxysmal movement disorder events during 8 weeks of maintenance treatment.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

3 STUDY DESIGN

As background for the statistical methods presented below, this section provides an overview of the study design. The protocol is the definitive reference for all matters discussed in what follows in this section.

3.1 Overall Study Design and Plan

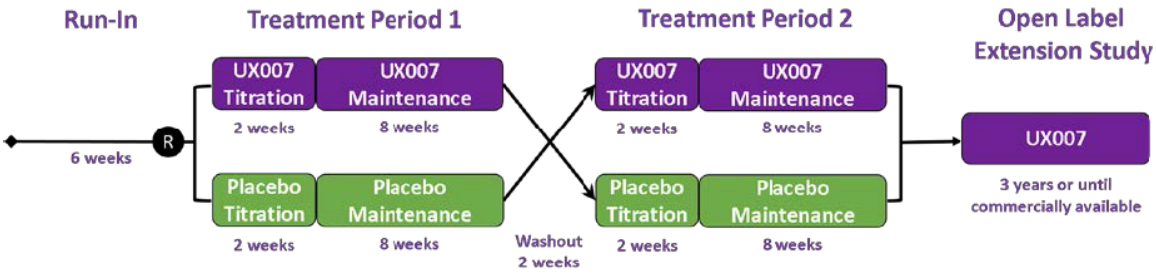
UX007G-CL301 is a randomized, double-blind (DB), placebo-controlled, crossover study to assess the efficacy and safety of UX007 in the treatment of movement disorders associated with Glut1 DS. The study will enroll approximately 40 pediatric, adolescent, and adult subjects who are not on ketogenic diet (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 electronicGlut1 DS movement disorder diary; if the minimum criterion for number of events is not met, or subjects complete <80% of the daily electronicGlut1 DS movement disorder 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) to one of two treatment sequences (UX007/placebo or placebo/UX007). At Randomization, subjects will begin a 10-week double-blind Treatment Period I. At the end of Treatment Period I, subjects will discontinue treatment and begin a 2-week washout period to minimize any potential carryover effect. Subjects will crossover to the second, double-blind treatment assignment (placebo to UX007, UX007 to placebo) for an additional 10 weeks during Treatment Period II. Dosing will be initiated in both treatment periods using a 2-week titration schedule until the subject has reached his/her age-related target dose. 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. At the end of the blinded crossover period (Week 22), all subjects will have the option of rolling into the Open-Label Extension (OLE) Period, to continue UX007 treatment for up to 3 years or until approval. A safety follow-up phone call will be conducted 30-35 days after the last dose of UX007G-CL301 study drug.

Figure 1 provides a schematic of the study design.

Figure 1: UX007G-CL301 Study Schematic



3.2 Discussion of Study Design, Including Choice of Control Group

The choice of the crossover 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).

Given 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 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 UX007 (Mochel et al. 2015). The proposed Phase 3 study is designed to assess the efficacy and safety of UX007 in reducing the frequency of disabling paroxysmal movement disorder events in Glut1 DS patients who are not on KD.

3.3 Study Duration

Subject participation during the DB Treatment Period (including the Run-in Period, Baseline, Treatment Period I, Washout, and Treatment Period II) will be 28 weeks in duration; the OLE 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-CL301 study drug. The last subject's safety follow-up phone call is the defined end-of-study time point.

The schedule of assessments is shown in Section 10.2 Appendix B and Section 10.3 Appendix C.

3.4 Randomization and Stratification Factors

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. Subjects will be randomized in a 1:1 ratio to UX007/Placebo or Placebo/UX007 treatment sequence via an Interactive Web Randomization System (IWRS) based on a randomization schedule developed by an independent third-party vendor to maintain blinding. The randomization procedure will be performed without stratification.

3.5 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 post the double-blind portion of the study database is locked. 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.

The Investigator and site personnel will remain blinded to the randomization code during the double-blind portion of the study. Treatment assignment for an individual subject should be unblinded by the Investigator only in an emergency e.g., event concerning subject safety, and only if knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. The Investigator should contact the medical monitor before unblinding, when possible, but priority should be given to the safety of the subject.

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. Detailed blinding procedures are specified in the study protocol.

3.6 Sample Size Considerations

The primary efficacy parameter is number of disabling paroxysmal movement disorder events observed during the Maintenance Period of Treatment Periods I and II. 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 at the two-sided 5% significance level. This sample size assumption incorporates a projected discontinuation rate of 15%.

3.7 Interim Analysis

There is no interim analysis planned for this study.

3.8 Primary Analysis

The primary analysis will occur when all subjects have completed the DB Treatment Period, or withdrawn from the study during the DB Treatment Period, whichever comes earlier.

3.9 Final Analysis

The final analysis will occur when all subjects have completed the OLE Period, or withdrawn from the study, whichever comes earlier.

Additional analyses may be performed after primary analysis during the course of the study at the discretion of the Sponsor.

3.10 Data Monitoring Committee (DMC)

An independent DMC with 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. The DMC may also provide advice to Ultragenyx in any determination of whether study enrollment should be paused or if the study should be halted. The detailed roles and responsibilities of the DMC are specified in the DMC Charter.

4 STUDY ENDPOINTS AND COVARIATES

All data are collected according to the schedule of assessments (Section 10.2 Appendix B and Section 10.3 Appendix C).

4.1 Primary Efficacy Endpoints

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

4.2 Secondary Efficacy Endpoints

- Total duration of disabling paroxysmal movement disorder events during maintenance phase, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary
- Change from period baseline to treatment week 10 in 12 Minute Walk Test (12MWT) distance
- Patient/caregiver Clinical Global Impression – Improvement (CGI-I) score at treatment week 10
- Change from period baseline to treatment week 10 in Patient Reported Outcomes Measurement Information System (PROMIS) scores (domain scores)
- Change from period baseline to treatment week 10 in the following Cambridge Neuropsychological Test Automated Battery (CANTAB) scores (assessed at select sites)
  - Spatial Span (SSP):
    - Span Length (SSPSLF)
  - Spatial Working Memory (SWM):
    - Between Errors (SWMBE48)
    - Strategy (SWMS68)
  - Paired Associates Learning (PAL):
    - Total Errors (Adjusted) (PALTEA)
    - First Trial Memory Score (PALFTMS)

4.3 Exploratory Efficacy Endpoints

- Change from period baseline in performance score and in satisfaction score as assessed by Canadian Occupational Performance Measure (COPM) at treatment week 10
- Physician CGI-I score at treatment week 10
- Change from period baseline in physician Clinical Global Impression-Severity (CGI-S) score at treatment week 10
- Change from study baseline to treatment week 10 in mean daytime activity, mean nighttime activity, and percent time in moderate or higher intensity activity as measured by a wrist-worn actigraphy device at select study sites where feasible
- Frequency of disabling paroxysmal movement disorder events over time throughout the three-year OLE period.
- Total duration of disabling paroxysmal movement disorder events over time throughout the three-year OLE period
- PK data for UX007 metabolites
- Efficacy Endpoints during the three-year OLE period: 12MWT, Patient/caregiver CGI-I, CANTAB, Physician CGI-I, Physician CGI-S, performance score and satisfaction score as assessed by COPM, PROMIS scores (domain scores)

4.4 Safety Endpoints

- Adverse events (AEs), including the subject incidence of AEs, treatment related AEs, serious adverse events (SAEs), AEs leading to discontinuation and fatal AEs
- Vital signs
- Clinical laboratory test results
- Electrocardiogram (ECG)
- Suicidal ideation and behavior assessment as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)

4.5 Covariates

For the analysis of covariate (ANCOVA) analysis, baseline (study baseline or period baseline) of the response variable will be included as the covariates, whenever appropriate. Sequence and period will also be included as the covariates, when analyzing the DB treatment data.

4.6 Subgroups

Using information from the Ketogenic Diet CRF form, the following subgroups are identified to examine any potential treatment effect.

1. Subjects who have never tried a prescribed diet plan to manage Glut1 symptoms.

2. Subjects who have tried a prescribed diet plan to manage Glut1 symptom and the most recent prescribed diet (KD/Modified Atkins Diet/other) was discontinued due to lack of efficacy.

3. Subjects who have tried a prescribed diet plan to manage Glut1 symptom and the most recent prescribed diet (KD/Modified Atkins Diet/other) was discontinued for a reason or reasons other than lack of efficacy.

5 DEFINITIONS

5.1 Study Day

- If the assessment date is on or after the first dose date of investigational product:
- Study day = (assessment date – first dose date of investigational product + 1)
- If the assessment date is prior to the first dose date of investigational product:
- Study day = assessment date – first dose date of investigational product

5.2 Study Week/Treatment Week

Study weeks are the time points recorded on CRF.

For the DB treatment period, treatment weeks are defined as:

- For subjects randomized to UX007/Placebo group
  - UX007 treatment week=study week
  - Placebo treatment week=study week-12
- For subjects randomized to Placebo/UX007 group
  - Placebo treatment week=study week
  - UX007 treatment week=study week-12

5.3 Duration of Exposure

- Duration of exposure to Investigational Product (IP) (Placebo or UX007), in days, is defined as:
  - During the DB Treatment Period: defined as last dose date of IP in the corresponding treatment period of the DB Period – first dose date of IP in the corresponding treatment period of the DB Period + 1 day
- Duration of exposure to UX007, in days, is defined as:
  - During the OLE Period is defined as last dose date of UX007 in OLE Period – first dose date of UX007 in OLE Period + 1 day
  - During the whole study is defined as the sum of the duration of exposure to UX007 in days during the DB Treatment Period and the duration of exposure to UX007 in days during the OLE Period

5.4 Age

Age will be derived based on the informed consent date as Age = (Inform Consent Date – Birth Date +1)/365.25. Age will be rounded down and keep 1 decimal place. When date of birth is missing, then age recorded on case report form (CRF) at time of informed consent will be used.

5.5 Baseline

- Movement Disorder:

Study baseline for movement disorder frequency as recorded by the subject/caregiver in diary will be normalized to a 4-week rate as

$$\frac{\text{total number of movement disorder events during the 6 weeks run-in period} \times 28}{\text{number of days with diary data during the 6 weeks run-in period}}$$

Study baseline for total duration of movement disorder in hours will be normalized to a 4-week rate as

$$\frac{\text{total duration of movement disorders in hours during the 6 weeks run-in period} \times 28}{\text{number of days with diary data during the 6 weeks run-in period}}$$

- For other efficacy endpoints, study baseline is defined as the last non-missing assessment prior to or on the date of the first dose of investigational product
- For safety endpoints, study baseline is defined as the last non-missing assessment prior to or on the date of the first dose of investigational product

Period baseline is defined as the last non-missing assessment prior to or on the date of the first dose of investigational product for each DB treatment period. A value from the first treatment period will not be considered as the period baseline for the second treatment period.

5.6 Movement Disorder Frequency and Total Duration

For analyses, movement disorder frequency and total duration in hours will be normalized to a 4-week rate at each of the specified period:

$$\frac{\text{total number of movement disorders during the specified period} \times 28}{\text{number of days with diary data during the specified period}}$$

$$\frac{\text{total duration of movement disorders during the specified period} \times 28}{\text{number of days with diary data during the specified period}}$$

Mean duration in hours at each of the specified period is defined as:

$$\frac{\text{total duration of movement disorders during the specified period}}{\text{total number of movement disorders during the specified period}}$$

The percentage of movement disorder free days is defined as

$$\frac{\text{total number days with of zero movement disorder}}{\text{number of days with diary during the specified period}} * 100\%$$

5.7 Percent Predicted Six Minute Walk Test (6MWT) Distance

To calculate the percent predicted 6MWT value, the following formulas will be applied (Geiger et al. 2007) for subjects aged <20 years old at randomization:

$$For\ Males: X_i = \frac{X_{0i}}{196.72 + (39.81 * Age) - (1.36 * Age^2) + (132.28 * Height)} * 100$$

$$For\ Females: X_i = \frac{X_{0i}}{188.61 + (51.50 * Age) - (1.86 * Age^2) + (86.10 * Height)} * 100$$

Where:
X_i = The percent predicted 6MWT result at time *i* for subject X
X_{0i} = The 6MWT (m) result at time *i* for subject X

To calculate the percent predicted 6MWT value, the following formulas will be applied (Gibbons et al. 2001) for subjects aged ≥20 years old at randomization:

$$X_i = \frac{X_{0i}}{868.8 - (2.99 * Age) - (74.7 * Women)} * 100$$

Where:
X_i = The percent predicted 6MWT result at time *i* for subject X
X_{0i} = The 6MWT (m) result at time *i* for subject X
Women = an indicator variable: equal to 1 if the subject is female and 0 if male

The percent predicted 6MWT formulas will use the subject's height (m) and age at the randomization visit throughout the study duration.

5.8 PROMIS Scores

The PROMIS questionnaires have been developed from the Adult and Pediatric PROMIS Item Banks (Broderick et al. 2013) (NIH 2015). Self- and proxy-report versions are available and use is based on participant age and cognitive ability. The responses collected from PROMIS questionnaires will be uploaded to the web-based application, HealthMeasures Scoring Service, to obtain the final T-scores for each domain listed below (http://www.healthmeasures.net/score-and-interpret/calculate-scores).

For adults, T-scores will be derived for the following domains:

- physical function
- fatigue
- sleep disturbance
- pain interference
- cognitive function
- ability to participate in social roles and activities
- anxiety

For pediatric subjects (under the age of 18), T-scores will be derived for the following domains,

- mobility
- upper extremity
- fatigue
- pain interference
- peer relationships

5.9 Physician and Patient/Caregiver CGI Scales

Physician CGI-S score and patient/caregiver CGI-S score use a 4-point Likert scale (1 = Normal to 4 = Severe) to rate disease severity.

Physician CGI-I score and patient/caregiver CGI-I score use a 7-point Likert scale (1 = Very much better to 7 = Very much worse) to record the degree of change in clinical status.

5.10 COPM

Up to five most important occupational performance problems as reported by the subject/parent/caregiver at the Study Week 0 visit will be scored using a scale of 1-10 (1 = poor performance and low satisfaction to 10 = very good performance and high satisfaction) to provide a Performance score and a Satisfaction score for each of the occupational performance problems.

The performance or satisfaction score can be derived as:

$$\frac{\text{Sum of performance or satisfication scores}}{\text{Number of problems that were actually answered}}$$

5.11 Activity measurements by Actigraphy Device

A wrist-worn activity monitor (actigraphy device) will assess the impact of Glut1 DS on activity at select study sites, where feasible. The endpoints 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. The endpoints are defined as following:

Mean daytime activity: Average activity count during worn epochs between the hours of 10 a.m. and 8 p.m in the last 10 days of the specified period. If there are no worn epochs, the value will be -1

Mean nighttime activity: Average activity count during worn epochs between the hours of 12 a.m. and 5 a.m in the last 10 days of the specified period. If there are no worn epochs, the value will be -1

Percent time in moderate or higher intensity activity: The ratio of total minutes in moderate to vigorous physical activity to total wear minutes. This will be -1 if there no wear minutes.

6 ANALYSIS POPULATIONS

6.1 Screened Population

The Screened Population will consist of all subjects who underwent at least one Screening Visit and received a subject identification number.

6.2 Full Analysis Set

The Full Analysis Set will consist of all enrolled subjects who received at least one dose of investigational product. Subjects will be analyzed according to randomized treatment sequence.

6.3 Per Protocol Set

The Per Protocol Set will consist of all subjects in the Full Analysis Set who meet the following criteria:

- The percentage of days with non-missing movement disorder diary is at least 80% for the planned run-in period duration (6 weeks) and each of the two planned maintenance period durations (8 weeks).
- The percentage of days with non-missing doses is at least 80% for each of the two planned maintenance period durations (8 weeks).
- After titration period, the target dose (25%) of UX007 is reached for at least one day for the planned maintenance periods.

6.4 Safety Analysis Set

The Safety Analysis Set will consist of all enrolled subjects who received at least one dose of investigational product. Subjects will be analyzed according to the actual treatment sequence.

7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

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

7.2 Handling of Missing and Incomplete Data

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

Unless specified otherwise, only the observed data will be presented. When a change from baseline is assessed, only patients with a baseline and at least one post-baseline measurement will be included in the analysis.

7.2.1 Missing Date Imputation for Medical History

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

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

7.2.2 Missing Date Imputation for AEs and Concomitant Medications

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

<u>Missing Start Dates</u>

- If the day is unknown, then:
  - If the month and year match the start date month and year of the first dose of investigational product in this study, then impute as the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If the month is unknown, then:
  - If the year matches the start date year of the first dose of investigational product date in this study, then impute as the month and day of the first dose date in this study.
  - Otherwise, assign ‘January’.

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

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

Missing Stop Dates and Not Ongoing

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December'.
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing. If the AE has been recorded as resolved/recovered, all efforts should be made to obtain the date from the Investigator.

If the resulting end date is after the date of study completion/discontinuation/data cutoff, set the imputed end date as close to the date of study completion/discontinuation/data cutoff as possible without overwritten existing information.

7.3 Visit Time Windows

Table 1 presents the assigned target study day and study day window for each study period. Movement disorder frequency and duration recorded on diary will be mapped to specified period according to Table 1 and actual visit days. For other scheduled efficacy and safety assessments the visit window assigned and the corresponding target treatment days during which an actual visit may occur is specified in Table 2.

Table 1: Visit Mapping Window for Movement Disorder Diary

Period		Planned Duration	Target Study Day	Study Day Window
Run-In		6 weeks	[-42, 0]	<1
DB Treatment Period I	Titration	2 weeks	[1,15]	[1, 15]
	Maintenance	8 weeks	[16,71]	For subjects who entered into washout period: [study day of first dose in Treatment Period I+15, the end of Treatment Period I]; For subjects who did not enter into washout period: ≥ study day of first dose in Treatment Period I+15
Washout		2 weeks	[72,85]	For subjects who entered into Treatment Period II[1]: [the end of Treatment Period I+1, study day of first dose in Treatment Period II-1]; For subjects who did not enter into Treatment Period II: ≥ the end of Treatment Period I +1
DB Treatment Period II	Titration	2 weeks	[86,99]	[study day of first dose in Treatment Period II, study day of first dose in Treatment Period II+14]
	Maintenance	8 weeks	[100,155]	For subjects who entered into extension period: [study day of first dose in Treatment Period II+15, the end of Treatment Period II]; For subjects who did not enter into OLE period: ≥ study day of first dose in Treatment Period II+15
OLE Period	Week 34	12 weeks	[156, 281]	[study day of first OLE dose date, 281]
	Week 46	12 weeks	[282,365]	[282,365]
	Week 58	12 weeks	[366, 449]	[366, 449]
	Week 70	12 weeks	[450, 533]	[450, 533]
	Week 82	12 weeks	[534, 617]	[534, 617]
	Week 94	12 weeks	[618, 701]	[618, 701]
	Week 106	12 weeks	[702, 785]	[702, 785]
	Week 118	12 weeks	[786, 869]	[786, 869]
	Week 130	12 weeks	[870, 953]	[870, 953]
	Week 142	12 weeks	[954, 1037]	[954, 1037]
	Week 154	12 weeks	[1038, 1121]	[1038, 1121]
	Week 166	12 weeks	[1122, 1205]	[1122, 1205]
	Week 178	12 weeks	≥1206	≥1206

[1] Enter into treatment Period II is defined as subjects having taken any Treatment Period II dosing
[2] Enter into OLE phase is defined as subjects having taken any OLE phase dosing.

Table 2: Visit Window for Other Scheduled Efficacy and Safety Assessments

Period	Study Week	Treatment Week	Target Day	Study Day Window
DB Treatment Period I	Study Week 0	Trt Week 0	1	≤1
	Study Week 2	Trt Week 2	15	[2, 15]
	Study Week 10	Trt Week 10	71	For subjects who entered into Treatment Period II[1]: [16, 78] For subjects who did not enter into Treatment Period II: ≥16
DB Treatment Period II	Study Week 12	Trt Week 0	85	[79, study day of first dose in Treatment Period II]
	Study Week 14	Trt Week 2	99	[study day of first dose in Treatment Period II+1, study day of first dose in Treatment Period II+15]
	Study Week 22	Trt Week 10	155	For subjects who entered into OLE period[2]: [study day of first dose in Treatment Period II+16, the end of Treatment Period II]; For subjects who did not enter OLE period: ≥study day of first dose in Treatment Period II+16
OLE Period	Study Week 34		239	[study day of first OLE dose date, 281]
	Study Week 46		323	[282,365]
	Study Week 58		407	[366, 449]
	Study Week 70		491	[450, 533]
	Study Week 82		575	[534, 617]
	Study Week 94		659	[618, 701]
	Study Week 106		743	[702, 785]
	Study Week 118		827	[786, 869]
	Study Week 130		911	[870, 953]
	Study Week 142		995	[954, 1037]
	Study Week 154		1079	[1038, 1121]
	Study Week 166		1163	[1122, 1205]
	Study Week 178		1247	≥1206

[1] Enter into treatment Period II is defined as subjects having taken any Treatment Period II dosing
[2] Enter into OLE phase is defined as subjects having taken any OLE phase dosing.

7.4 Unscheduled or Early Termination Visits

For an unscheduled visit that occurred after the first dose date of IP, the unscheduled visit will be mapped into the closest post-baseline study scheduled visit for the assessment based on the study day of the unscheduled visit, and the target study day of the scheduled visit of the assessment in the protocol. If the unscheduled visit has the equal distance to the 2 study scheduled visits, it will be mapped to the later one.

An unscheduled visit will only be mapped to a study visit within each study period during which it occurs. For example, if an unscheduled visit occurs during the Titration period of the DB Treatment Period I, it should be mapped to the study visit in the Titration period of the DB Treatment Period I.

When there are more than one measurements mapped to the same scheduled visit (including the original measurement taken from the scheduled visit), the measurement taken on the scheduled visit will be used if it is not missing, otherwise the one closest to the target day will be used. If more than one visit has the equal distance to the target day then the later one will be used. If more than one measurement is collected on the same day, use the time or the sequence number to select the latest record. For listings and shift tables, all data points will be included.

Early termination visit will follow the same rule for unscheduled visit as described above.

7.5 Software

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

8 STATISTICAL METHODS OF ANALYSES

8.1 General Principles

All statistical tests will be two-sided and tested at statistical significant level of 0.05. The statistical analyses will be reported using summary tables, figures, and data listings. Continuous variables will be summarized by number of subjects and mean, standard deviation (SD), standard error (SE) median, 25%th and 75%th quartile, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. All raw data obtained from the CRFs will be included in data listings.

8.2 Subject Accountability

The number and percentage of subjects in each of the study populations (Screened Population, Full Analysis Set, Per Protocol Set and Safety Analysis Set) will be summarized by treatment sequence. Subjects excluded from the analysis sets will be listed.

The number and percentage of subjects who complete each of the two double-blind treatment periods, who complete the OLE Period, and who prematurely discontinue will be presented by treatment sequence. The reasons for premature discontinuation from treatment as recorded on CRFs will be summarized by treatment sequence as well.

8.3 Protocol Deviations

Protocol deviations will be summarized for the Screened Population by treatment sequence and period. Both major and minor protocol deviations will be listed. The determination of major and minor protocol deviations will occur prior to unblinding.

8.4 Demographic and Baseline Characteristics

Summary statistics will be provided by treatment sequence for the Full Analysis Set for the following parameters:

- Age at informed consent
- Gender
- Ethnicity
- Race
- Age at Glut1 DS diagnosis

8.5 Disease Characteristics and Medical History

Summary statistics will be presented for the Full Analysis Set by treatment sequence and overall, for the following parameters:

- Duration of Glut1 DS symptom
- Glut1 DS mutation description
- Glut1 DS symptoms history including whether ongoing
- KD history and reason for KD discontinuation

Medical history will also be summarized by system organ class (SOC) and preferred term (PT) for the Full Analysis Set by treatment sequence.

8.6 Investigational Product Administration

8.6.1 Extent of Exposure

Exposure duration to the investigational product will be summarized by treatment for the Safety Analysis Set for the DB Treatment Period, and the whole study.

8.6.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the investigational product actually taken by a subject during that period in ml divided by the investigational product expected for the same period in ml multiplied by 100.

Descriptive statistics for dosing compliance will be summarized by treatment sequence and treatment for the Safety Analysis Set for the DB treatment and OLE Period. Number of days with non-missing dose will also be summarized by treatment sequence and treatment.

The percentage of subjects who reach target dose within 2 weeks of titration period will be summarized by treatment for the DB Treatment Period. Time to reach target dose will also be summarized by treatment.

8.6.3 Diet Diary Review

The following measures will be summarized by visit based on the 3-day Diet Diary Review:

- Average Study Drug Calories, as calculated as the average of the 3 entries for study drug
- Average Total Daily Calories

8.7 Prior and Concomitant Medication

Prior medication is defined as any medication started before the date of the first dose of investigational product.

Concomitant medication is defined as any medication taken on or after the date of the first dose of investigational product. A medication started before the date of the first dose of investigational product and also taken after the date of first dose of investigational product will be counted both as a prior and concomitant medication.

Both prior and concomitant medications will be coded by drug name and therapeutic class using World Health Organization (WHO) Drug Dictionary. Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term by treatment sequence for the Safety Analysis Set. Similarly, concomitant medications will be summarized by treatment sequence for the Safety Analysis Set for the double blind treatment periods and the whole study.

8.8 Efficacy Analyses

Efficacy analyses will be based on the Full Analysis Set, unless otherwise specified.
Section 10.1 Appendix A summarizes the analysis strategy for efficacy endpoints.
For weighted ANCOVA analysis, weight will be calculated by using number of non-missing diary days divided by the planned maintenance period duration (8 weeks). For Wilcoxon rank-sum test, the difference between responses of Treatment Period 1 and Period 2 will be ranked to make the non-parametric comparison between two treatment groups.

8.8.1 Analyses of Primary Efficacy Endpoint

The primary endpoint is the frequency of movement disorder events during the maintenance treatment period. In the event of electronic diary failure, the back-up paper diary might be used during the days with missing data from electronic diary. Combined electronic diary data and paper diary data will be used.

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.

After study unblinding, the normality assumption of ANCOVA model will be examined by using the Wilk-Shapiro test on the residuals from the ANCOVA model (Shapiro et al. 1965) When there is strong evidence suggesting that the normality assumption is not met (p value for Wilk-Shapiro test < 0.05) (Nornadiah 2011) (Yap et al. 2011), Wilcoxon rank-sum test will be considered as the primary analysis to assess treatment difference in movement disorder event frequency.

The following sensitivity analyses will be performed.

- To analyze the percent change from study baseline in the frequency of movement disorder during the maintenance period, the primary weighted ANCOVA model will be performed.
- Wilcoxon rank-sum test will be performed to assess treatment difference in movement disorder event frequency.
- The primary weighted ANCOVA based on the frequency of movement disorder events will be performed based on Per Protocol Set.
- In case paper diary is used as back up, sensitivity analysis excluding paper diary will be considered. The primary weighted ANCOVA based on the frequency of movement disorder events will be performed.
- If subjects discontinued during the 2-week titration period or missed one treatment period entirely, impute the movement disorder frequency during the maintenance period using the frequency during the titration period if titration period data is available, otherwise, the study baseline will be used to impute the movement disorder frequency during the maintenance period. Then the ANCOVA model based on the frequency of movement disorder events during maintenance phase will be performed, 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.

Movement disorder frequency during the maintenance period will also be summarized by the subgroup: reporting type of movement disorder diary (caregiver mode or subject mode).

The change from study baseline to maintenance phase in percentage of movement disorder free days will be analyzed using the primary weighted ANCOVA model.

Subgroup analysis by prior KD/Modified Atkins Diet will be conducted for the frequency of movement disorder events using the primary weighted ANCOVA model. If wilcoxon rank-sum test is used as the primary analysis to assess treatment difference in movement disorder event frequency, Wilcoxon rank-sum test will be used to perform the above subgroup analysis. Only point estimate and 95% CI will be presented for the subgroup analysis.

Test Carryover effect

The carryover effect will be tested as the significance of sequence effect. If the carryover effect is non-ignorable (p value < 0.05), analysis including only the first-period data will be considered.

8.8.2 Analyses of Secondary Efficacy Endpoints

If the primary analysis for the primary efficacy endpoint is statistically significant, then a hierarchically sequential hypothesis testing strategy will be implemented for the selected secondary efficacy endpoints in the following sequence at level 0.05 until first non-rejection:

- Total duration of movement disorder events during maintenance period
- Change from period baseline to treatment week 10 in 12MWT distance
- Patient/caregiver CGI-I score at treatment week 10

The primary analysis for the selected secondary efficacy endpoints are:

- For total duration of movement disorder events during maintenance period, the weighted ANCOVA model will be used with study baseline as a covariate, treatment sequence, treatment group, and period as fixed effects, and a random effect for subject within the sequence.
- For change from period baseline to treatment week 10 in 12MWT distance, the ANCOVA model will be used with period baseline as a covariate, treatment sequence, treatment group, period as fixed effects, and a random effect for subject within the sequence.
- For Patient/caregiver CGI-I score at treatment week 10, the ANCOVA model will be used with Patient/caregiver CGI-S study baseline as a covariate, treatment sequence, treatment group, period as fixed effects, and a random effect for subject within the sequence.
- After study unblinding, the normality assumption of ANCOVA model will be examined by using the Wilk-Shapiro test on the residuals from the ANCOVA model. When there is strong evidence that the assumption is not met (p value for Wilk-Shapiro test < 0.05), Wilcoxon rank-sum test will be considered as the primary analysis to assess treatment difference.

In addition, the following sensitivity analyses for total duration of movement disorder and 12MWT distance will be performed:

- The weighted ANCOVA based on total duration of movement disorder events during maintenance period will be performed based on Per Protocol Set. The mean duration of movement disorder events during maintenance period will be summarized.
- In case there is missing data in 12MWT distance, the following ordered procedure of missing data imputation will be considered: if the subject is missing post-baseline data at treatment week 10, impute the corresponding period baseline. If the subject is missing the second period baseline, impute the study baseline as the period baseline for the second period. If the subject is missing study baseline but has compete second period data, then only count the subjects for the second period

And then the primary ANCOVA model based on the 12MWT distance will be performed.

- Change from period baseline to treatment week 10 in the first 6MWT distance and percent predicted 6MWT distance will be analyzed by the ANCOVA model with period baseline as a covariate, treatment sequence, treatment group, period as fixed effects, and a random effect for subject within the sequence.

For the rest of the secondary endpoints, change from period baseline to treatment week 10 in PROMIS domain scores and change from period baseline to treatment week 10 in CANTAB scores, the primary analysis are:

- ANCOVA model with period baseline as a covariate, treatment sequence, treatment group, period as fixed effects, and a random effect for subject within the sequence will be used.
- After study unblinding, the normality assumption of ANCOVA model will be examined by using the Wilk-Shapiro test on the residuals from the ANCOVA model. When the assumption is not met (p value for Wilk-Shapiro test < 0.05), Wilcoxon rank-sum test will be considered as the primary analysis to assess treatment difference. If any of the domains fails the normality check, the Wilcoxon rank-sum test will be considered as primary analysis for all domains.

8.8.3 Analyses of Exploratory Efficacy Endpoints

An ANCOVA model with period baseline as a covariate, treatment sequence, treatment group, period as fixed effects, and a random effect for subject within the sequence, will be used to analyze change from period baseline to treatment week 10 in performance score and change from period baseline to treatment week 10 in satisfaction score as assessed by COPM.

An ANCOVA model with study baseline as a covariate, treatment sequence, treatment group, period as fixed effects, and a random effect for subject within the sequence, will be used to analyze the following other efficacy endpoints:

- Physician CGI-I score at treatment week 10, the Physician CGI-S study baseline will be used as an explanatory variable
- Physician CGI-S score at treatment week 10, the Physician CGI-S period baseline will be used as an explanatory variable
- Change from study baseline to treatment week 10 in mean daytime activity, mean nighttime activity, and percent time in moderate or higher intensity activity as measured by a wrist-worn actigraphy device at select study sites where feasible

Frequency, mean duration and total duration of disabling paroxysmal movement disorder events over time throughout the three-year OLE period will be summarized. Change from

study baseline in percentage of movement disorder free days during the three-year OLE period will also be summarized.

Efficacy Endpoints during the three-year OLE period including 12MWT, Patient/caregiver CGI-I, CANTAB, Physician CGI-I, Physician CGI-S, performance score and satisfaction score as assessed by COPM, PROMIS scores (domain scores) will be summarized and study baseline will be used.

8.9 Safety Analyses

All safety analyses will be performed using the Safety Analysis Set. Safety parameters will include AEs, clinical laboratory parameters, vital signs, ECG parameters, and other safety parameters. No statistical comparisons will be performed.

8.9.1 Adverse Events

Adverse events will be coded by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA). AEs during Run-In period will be summarized.

A treatment emergent adverse event (TEAE) will be considered and assigned to the treatment group (UX007 or Placebo) if the AE (classified by preferred term) start date occurs or worsens in severity on or after the first dose of study drug in the corresponding treatment period and before the first dose of study drug in the next treatment period. For example, an AE will be assigned to the treatment in Treatment Period I if it occurred during the wash out period. An AE that occurs within 30 days after the last dose of study drug in the last treatment period will be assigned to the last treatment period.

The incidence of subjects reporting TEAEs in each treatment and treatment sequence will be tabulated by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to study drug. If more than one event occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to the study drug.

The incidence of subjects reporting TEAEs by treatment and treatment period will also be summarized by SOC and PT for each of the following categories:

- All TEAEs
- Treatment related TEAEs
- Grade 3 or 4 TEAEs
- Serious TEAEs
- Serious and related TEAEs
- TEAEs leading to study discontinuation
- TEAEs leading to treatment discontinuation

- TEAEs leading to death

Exposure adjusted TEAE incidence is defined as total number of occurrences of an event summed across all subjects by treatment divided by the total exposure duration. A TEAE which occurred during the wash-out period will be considered and counted into the first treatment period. Exposure adjusted TEAE incidence will be summarize by treatment, and period.

Detailed listings for all AEs, TEAEs, serious TEAEs, AEs leading to study/treatment discontinuation, and death will also be generated.

8.9.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from study baseline values at each assessment time point will be presented by treatment sequence for clinical laboratory parameters specified in the protocol. Change from period baseline by treatment and treatment week during DB period will also be presented.

The clinical laboratory parameters include the following:

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

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) after study drug administration will be presented for each clinical laboratory measurement by treatment sequence and period.

Hy's Law criteria will be applied against test results. Subjects with serum total bilirubin >2 × ULN and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × ULN will be considered positive for Hy's law status. Shift tables will be produced by treatment sequence:

- Hy's Law negative at study baseline, remaining Hy's Law negative throughout the DB treatment period

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

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

8.9.3 Vital Signs

Descriptive statistics for observed values and changes from study baseline values at each visit will be presented by treatment sequence and period for the following vital signs:

- Temperature (°C)
- Respiration Rate (breaths/min)
- Heart Rate (beats/min)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Weight (kg)
- Head circumference (cm)

8.9.4 Electrocardiogram

The results from ECG (normal and abnormal) will be summarized.

8.9.5 Suicidal Ideation and Behavior

The number and percentage of subjects with suicidal ideation or suicidal behavior will be presented at study baseline and post-baseline by category, treatment sequence and period. If more than one suicidal ideation or suicidal behavior was reported for the same period/visit, the one with greatest severity will be used for the same period/visit in the summary.

8.10 PK Analyses

Plasma levels of UX007 metabolites will be summarized using descriptive statistics by study visit and treatment group. Standard non-compartmental analysis will be conducted to estimate PK parameters (such as Cmax, Tmax, AUC) for UX007 metabolites of importance when there are sufficient data points. Descriptive statistics will be provided for PK parameters for UX007 metabolites.

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10 APPENDICES

10.1 Appendix A. Efficacy Endpoint Summary Table

Endpoint	Approach	Statistical Method	Analysis Population	Missing Data Imputation (Yes/No)
Primary Endpoint				
Frequency of disabling paroxysmal movement disorder events during maintenance period	P	Weighted ANCOVA	FAS	No
	S	Wilcoxon Rank-Sum Test	FAS	No
		Weighted ANCOVA of the percent change from study baseline in the frequency of movement disorder during the maintenance period	FAS	No
		Weighted ANCOVA with Per Protocol Set	FAS	No
		Weighted ANCOVA (excluding back-up paper diary data)	FAS	No
		Weighted ANCOVA of the change from study baseline to maintenance phase in percentage of movement disorder free days	FAS	No
		ANCOVA	FAS	Yes
		Weighted ANCOVA with subgroups by prior KD/Modified Atkins Diet	FAS	No
Secondary Endpoints				
Change from period baseline to treatment week 10 in 12MWT distance	P	ANCOVA	FAS	No
	S	ANCOVA	FAS	Yes
		ANCOVA of change from period baseline to treatment week 10 in 6MWT distance and percent predicted 6MWT distance	FAS	No

Endpoint	Approach	Statistical Method	Analysis Population	Missing Data Imputation (Yes/No)
		ANCOVA of change from period baseline to treatment week 10 in percent predicted 6MWT distance	FAS	No
Change from period baseline to treatment week 10 in PROMIS scores	P	ANCOVA	FAS	No
Patient/caregiver CGI-I score at treatment week 10	P	ANCOVA	FAS	No
Total duration of disabling paroxysmal movement disorder events during maintenance period	P	Weighted ANCOVA	FAS	No

Endpoint	Approach	Statistical Method	Analysis Population	Missing Data Imputation (Yes/No)
Change from period baseline to treatment week 10 in CANTAB scores	P	ANCOVA	FAS	No
Other Efficacy Endpoints				
Percent change from study baseline in frequency of disabling paroxysmal movement disorder events over time	P	Descriptive Statistics	FAS	No
Percent change from study baseline in total duration of disabling paroxysmal movement disorder events over time	P	Descriptive Statistics	FAS	No
Physician CGI-S score at treatment week 10	P	ANCOVA	FAS	No
Physician CGI-I score at treatment week 10	P	ANCOVA	FAS	No
Change from study baseline to treatment week 10 in mean daytime activity, mean nighttime activity, and percent time in moderate or higher intensity activity	P	ANCOVA	FAS	No
Change from period baseline to treatment week 10 in COPM performance and satisfaction scores	P	ANCOVA	FAS	No
FAS = Full Analysis Set; P = Primary; S = Sensitivity.				

10.2 Appendix B. Schedule of Events (Screening; Run-in; Period I; Washout; and Period II)

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

10.3 Appendix C. 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.