STATISTICAL ANALYSIS PLAN

Title	**An Open-label Extension Study to Assess the Long-term Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome**
Protocol:	**UX007G-CL202**
Investigational Product:	**UX007 (Triheptanoin)**
Phase:	**2**
Sponsor:	**Ultragenyx Pharmaceutical Inc.** **60 Leveroni Court** **Novato, CA, USA 94949**
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Version Number:	**1.0**

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
CNS	Columbia Neurological Scores
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
GEE	generalized estimating equations
GGT	Gamma-glutamyl transpeptidase
KD	Ketogenic Diet
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCS	Physical Component Summary
PHS	Psychosocial Summary Score
PK	Pharmacokinetics
PSS	Physical Summary Score
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-10	Short Form-10
SF-12	Short Form-12
SI	Le Système International d'Unités (International System of Units)
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

ULN	Upper Limit of Normal
UX007	Triheptanoin
WBC	White Blood Cell
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-CL202 original protocol and all amendments through Protocol Amendment 3 dated 20 Sep 2017. This is the original version of SAP for this study. Changes from these guidelines must be substantiated by sound statistical reasoning and documented in the clinical study report (CSR).

2 STUDY OBJECTIVE(S)

2.1 Primary Objective

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

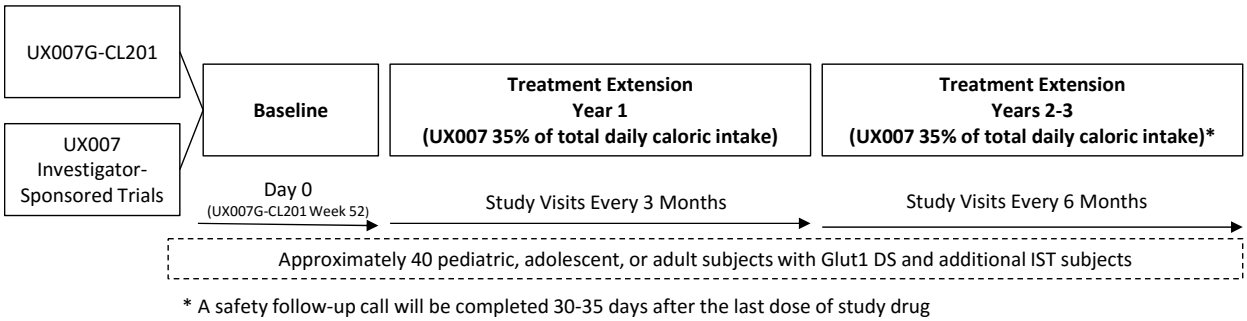
2.2 Secondary Objectives

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

3 STUDY DESIGN

UX007G-CL202 is an open-label, single-arm, multicenter extension study to assess the long-term safety and efficacy of UX007 in Glut1 DS. The study will enroll up to 40 pediatric, adolescent, and adult Glut1 DS subjects who have completed the UX007G-CL201 study and, at the discretion of the Sponsor, additional subjects who have participated in other clinical studies, Investigator-sponsored Trials (ISTs), or expanded access/compassionate use treatment programs. Figure 1 provides a schematic of the study design.

Figure 1: UX007G-CL202 Study Schema



For continuing UX007G-CL201 subjects, the Week 52 visit of that study may be conducted in conjunction with the Baseline visit for this study to avoid duplication of assessments. Following the Baseline visit, subjects will return to the study site at 3-month intervals from Baseline during Year 1 of the Treatment Extension, and 6-month intervals from Baseline during Years 2 and 3. Phone calls will take place 3-months between scheduled study site visits during Years 2 and 3 to collect adverse events and concomitant medications updates and to inquire about study drug consumption and remaining supply; in lieu of the phone call, subjects may also visit the clinic at the study site's discretion. Additionally, optional study site visits may occur 3-months between scheduled study site visits during Years 2 and 3 to allow subjects to attain study drug as needed at the request of the Investigator. A Safety Follow-up Phone Call will be conducted 30-35 days after last dose of study drug. The last subject's Safety Follow-up Phone Call is the End-of-study Time Point. Subjects will record seizure occurrence in a diary throughout the study; diet diaries will also be completed by the subject for the 3 days preceding each scheduled visit after Baseline. Overnight electroencephalograms (EEG) will be conducted in all subjects to monitor absence seizures. Safety assessments and a clinical neurological evaluation will further enable the characterization of long-term safety and maintenance of effect. Metabolites of UX007 in the blood will also be assayed.

3.1 Study Population

The study will be conducted in pediatric, adolescent, and adult Glut1 DS patients (aged at least 1 year at the time of informed consent) who have successfully completed the associated Phase 2 study (UX007G-CL201) or, at the discretion of the Sponsor, additional subjects who

participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs. Enrollment may include subjects from neighboring countries where clinical sites are located. Appropriate local or country requirements will be followed. All subjects in this study will have prior treatment exposure to UX007/triheptanoin. Refer to the protocol for detailed inclusion and exclusion criteria.

3.2 Dosage and Administration

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

3.3 Blinding and Randomization Methods

Not applicable.

3.4 Stratification Factors

Not applicable.

3.5 Sample Size Considerations

This study will enroll up to 40 pediatric, adolescent, and adult Glut1 DS subjects who have completed the UX007G-CL201 study and, at the discretion of the Sponsor, additional subjects from participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs. The sample size is intended to provide the maximum amount of information regarding UX007 long-term safety, along with indicators of sustained efficacy and durability of response in Glut1 DS patients.

3.6 Interim Analysis

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

3.7 Data Monitoring Committee

Not applicable.

4 STUDY ENDPOINTS AND COVARIATES

All data are collected according to the schedule of assessments (Appendix B).

4.1 Safety Endpoints

- Subject incidenceand severity of Adverse events (AEs) and serious adverse events (SAEs)
- Subject incidence of treatment related AEs, AEs leading to discontinuation, fatal AEs, and Gastrointestinal AEs using the standardized MedDRA query (SMQ) as listed in Appendix C.
- Prior and concomitant medication
- Observed value of vital signs and weight during the study
- Observed value of clinical laboratory test results and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside of reference ranges) and/or clinically significant abnormalities
- The number and percentage of subjects with suicidal ideation and behavior assessment as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)
- Physical examination
- Pregnancy testing if applicable

4.2 Efficacy Endpoints

- Reduction from baseline in frequency of seizures (normalized to a 4-week rate) during the study: Observable seizures from the diary will be used for Observable Seizures Subjects. For Absence Seizures Only Subject (See Section 5.7), the absence EEG data measured at the scheduled visit will be used.
- Observed value and reduction from baseline in frequency of observable seizure and absence seizure (normalized to a 4-week rate) by seizure diary
- Observed value and reduction from baseline in frequency of absence seizure and non-absence seizure (normalized to a 24-hour rate) by EEG
- Observed value and change from baseline in CNS total score
- Observed value and change from baseline in SF-10 summary scores
- Observed value and change from baseline in SF-12 domain/summary score
- Plasma levels of UX007 metabolites

4.3 Potential Covariate(s)

Not applicable.

5 DEFINITIONS

5.1 Classification of Subjects

The following grouping of subjects will be applied in analysis:

- Rollover subjects: include UX007G-CL201 study rollover subjects.
- Non-Rollover subjects: include all other subjects including IST and expanded access/compassionate use subjects.

5.2 Study Day 1

For all subjects, study day 1 is defined as the day of the first UX007 dose during study UX007G-CL202.

5.3 Baseline

For Rollover subjects:

The baseline defined in UX007G-CL201 study will be used for UX007G-CL202 study.

For Non-Rollover subjects:

In general, assessment performed on or prior to Month 0 visit (See Section 7.2.5, **Error! Reference source not found.**) in UX007G-CL202 study will be considered as study baseline for Non-Rollover subjects. The initial baseline (assessment prior to initial dose of UX007) is not available for Non-Rollover subjects.

5.4 Duration of Exposure

Duration of exposure to UX007, in days is defined as:

The last dose date of UX007 in UX007G-CL202 study – Study Day 1 + 1 day

5.5 Age

Unless specified, age will be derived based on the informed consent date as Age = (Inform Consent Date in UX007G-CL202 study – 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.

5.6 Classification of Observable Seizures and Absence Seizures

Table 1 shows the seizure classifications that are distinguished in the seizure diary, and which are counted towards study inclusion criteria and when deriving the observable seizures endpoints.

Table 1: Seizure Classification by Diary

Seizure Code (Diary)	Seizure Classification	Counted Towards Inclusion Criteria	Counted as Observable Seizure	Counted as Absence Seizure
A	Generalized Tonic-Clonic	X	X	
B	Generalized Tonic	X	X	
C	Generalized Clonic	X	X	
D	Generalized Atonic	X	X	
E	Partial/Focal with Secondary Generalization	X	X	
F	Myoclonic	X	X	
G	Myoclonic (Astatic) Atonic	X	X	
H	Myoclonic Tonic	X	X	
I	Complex Partial/Focal	X	X	
J	Simple Partial/Focal Motor	X	X	
K	Simple Partial/Focal Sensory		X	
L	Simple Partial/Focal Psychological		X	
M	Typical Absence	X [*]		X
N	Atypical Absence	X [*]		X
O	Absence with Special Features (Myoclonic absence)	X [*]		X
P	Absence with Special Features (Eyelid myoclonia)	X [*]		X
Q	Unclassified (Inc. epileptic spasms)			
UNK	Unknown			

[*] Note that for the 3 subjects in UX007G-CL201 study PPD seizure codes MNOP were not counted towards study inclusion criteria because they were randomized prior to the implementation of Protocol Amendment 3.

See Table 2 below for the list of absence seizure types that are counted.

Table 2: Seizure Classification by EEG

Label	Definition	Absence Seizure	Non-absence Seizure
GenTC-BMS	Generalized Tonic-Clonic		X
GenT-BMS	Generalized Tonic		X
GenC-BMS	Generalized Clonic		X
Partial-BMS	Partial		X
AbsenceAwake-BMS	Absence Awake (≥10sec)	X	
AbsenceSleep-BMS	Absence Sleep (≥10sec)	X	
IndetAbsenceAwake-BMS	Indeterminate Absence Awake (3-10sec)	X	
IndetAbsenceSleep-BMS	Indeterminate Absence Sleep (3-10sec)	X	
Myoclonus-BMS	Myoclonus		X

5.7 Classification of Subjects at Baseline by Seizure Type for Rollover Subjects

For UX007G-CL201 rollover subjects, the classification of subjects defined at randomization during UX007G-CL201 study will be used.

- Observable Seizures Subject: a subject who meets any of the following:
  - Observable seizure frequency (types A, B, C, D, E, F, G, H, I, J, K and L; see Section 5.6: Table 2) greater than or equal to 4 during the baseline period.
  - Observable seizure frequency less than 4 at randomization and absence seizure frequency less than 4 during the baseline period
- Absence Seizures Subject: a subject who meets any of the following:
  - has seizure types M, N, O or P (see Section 5.6: Table 2) recorded on the seizure diary during the baseline period
  - has absence seizures documented on the screening EEG
  - Absence seizure frequency (see Section 5.6, Table 2 and Section 5.8.2) greater than 0 during the baseline period

All subjects will either be an Observable Seizures Subject, an Absence Seizures Subject, or both. Since there is potential overlap, the following definitions are used to classify enrolled subjects into three mutually exclusive groups:

- Observable Seizures Only Subject: a subject who is an Observable Seizures Subject *but not an Absence Seizure Subject*
- Absence Seizures Only Subject: a subject who is an Absence Seizures Subject *but not an Observable Seizure Subject*
- Both Seizures Subject: a subject who is both an Observable Seizures Subject and an Absence Seizure Subject

Classification by seizure type at baseline is not defined for Non-Rollover subjects since all subjects in UX007G-202 study had prior treatment exposure to UX007 and there is no seizure diary measurement data prior to the initial UX007 treatment for Non-Rollover subjects.

5.8 Derived Seizure Efficacy Variables

5.8.1 Observable/Absence Seizure Frequency by Diary

Observable/Absence seizure frequency from the diary (normalized to a 4-week rate), is defined as:

$$\text{Observable/Absence Seizure Frequency} = \frac{\text{Total number of seizures}}{\text{Number of days observed}} \times 28$$

See Section 5.6, Table 2 for the list of observable/absence seizure types from diary that are counted. For analyses, observable/absence seizure frequency from the diary will be defined for every 3 month during Year 1 and every 6 month during Year 2 and 3. Refer to Section 7.2.5, Table 3 for visit window mapping for seizure frequency by diary.

5.8.2 Absence/Non-absence Seizure Frequency by EEG

The absence/non-absence seizure frequency from EEG (normalized to a 24-hour rate) is defined as:

$$\text{Absence/non-absence Seizure Frequency} = \frac{\text{Total number of seizures}}{\text{Number of hours observed}} \times 24$$

See Section 5.6, Table 2 for the list of absence/non-absence seizure types that are counted. Refer to Section 7.2.5, Table 3 for visit window mapping for seizure frequency by EEG.

5.9 Columbia Neurological Score (CNS) total score

The CNS is the sum of scores for the following domains: Weight (max=1), Height (max=1), Head Circumference (max=1), General Medical Exam (max=13), Funduscopic Exam (max=4), Cranial Nerves (max=12), Stance & Gait (max=7), Involuntary Movements (max=7), Sensation (max=3), Cerebellar Function (max=8), Muscle Bulk, Tone & Strength (max=6), Myotatic Reflexes (max=10), Toe Sign (max=2), Other Findings (max=1). The CNS is only scored when all domains are measured and ranges from 0 (abnormal exam) to 76 (normal exam). Higher scores are associated with higher neurological function.

5.10 SF-10 Health Survey

The SF-10 will be administered to caregivers of subjects aged 5 through 17 years. Responses are used to generate 2 component summary scores: Physical Summary Score (PSS) and the Psychosocial Summary Score (PHS).

The T-score Based scoring (described in Section 5.11) is used to score the SF-10 Health Survey for Children summary scales. The scale scores have been centered so

that a score of 50 corresponds to the average score in a comprehensive 2006 sample (a combination of general population and supplemental disability and chronic condition samples).

5.11 SF-12 Health Survey version 2

The SF-12 Health Survey version 2 is assessed for adults 18 years of age and older. Eight domain scores (Physical Functioning, Role Limitations due to Physical Health, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotions Problems, and Mental Health) are calculated from raw scores. And additionally, the domain scores are used to generate 2 component summary scores: physical health (PCS) and mental health (MCS).

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

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

T-score based scoring method scores the data in relation to U.S. general population t-scores. Therefore, all scores obtained that are below 50 can be interpreted as below the U.S. general population t-score and scores above 50 can be interpreted as above the U.S. general population t-score.

6 ANALYSIS POPULATIONS

Full Analysis Set (FAS): consists of all enrolled subjects who received at least one dose of investigational product during the study.

Full Analysis Set – SF-10 (FAS – SF-10): consists of the subset of subjects in the full analysis set who had a non-missing baseline.

Full Analysis Set – SF-12v2 (FAS – SF-12v2): consists of the subset of subjects in the full analysis set who had a non-missing baseline.

7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

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

7.2 Handling of Missing and Incomplete Data

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

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

For efficacy analyses related to seizure diary or EEG, the following imputation rules will be applied for subjects with incomplete diary/EEG data,

- For subjects who have incomplete diary data, observable/absence seizure frequency will be calculated by averaging over the days with complete diary data during the corresponding visit period.
- For subjects who have incomplete EEG, absence/non-absence seizure frequency will be calculated by averaging over the time that is complete during the corresponding visit time, even if the EEG is not done overnight.

7.2.1 Missing Date of the Last Dose of Investigational Product

When the date of the last dose of investigational product is missing for a subject, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last visit date will be used as the last dose date.

7.2.2 Missing Medical History Related Dates (eg, diagnosis date) or Birth Dates

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

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

7.2.3 Missing Date Imputation for Adverse Events and Concomitant Medications

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

Missing Start Dates

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

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

Missing Stop Dates 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

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

7.2.4 Missing Causal Relationship to Investigational Product for Adverse Events

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

7.2.5 Visit Time Windows

For all scheduled efficacy and safety assessments except seizure diary, the visit window assigned and the corresponding target treatment days during which an actual visit may occur is specified in Table 3.

Termination visit for subjects who didn't complete the study, and unscheduled visits will be mapped to the closest post baseline scheduled visits if the scheduled visits are missing. If there are more than one unscheduled/end of study visits mapped to the same window, the one closer 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 visits on the same day, use the time or the sequence number to select the later record. For listings and shift tables, all data points will be included. For assessments where both the planned study visit and an unscheduled visit or early termination visit corresponding to that study visit are both available, the planned study visit will be used for the analysis.

In general, all summary tables by visit include all scheduled assessments per schedule of assessments. For seizure diary data to measure, it will be mapped to time period between the visit time points as specified in Table 4 and will be used to define observable seizure frequency (refer to Section 5.8.1). If a subject misses a visit, then the expected visit date will be used in place of the actual visit date to define observable seizure frequency. Expected visit date is the date of the previous visit + the expected number of days between the previous visit and the missing visit. If the previous visit is also missing, then the expected date of the previous visit would be used instead.

Table 3: Visit Time Windows for Scheduled Efficacy and Safety Assessments

Period	Visit	Scheduled Visit Day	Window
Treatment Year 1	Month 0	Day 1	Days ≤ 1
	Month 3	Day 92	Days [2, 138]
	Month 6	Day 184	Days [139, 230]
	Month 9	Day 276	Days [231, 322]
	Month 12	Day 368	Days [323, 414]
Treatment Year 2 - 3	Month 18	Day 552	Days [507, 598]
	Month 24	Day 736	Days [691, 782]
	Month 30	Day 920	Days [875, 966]
	Month 36	Day 1104	Days [1059, 1150]

*Number of days in 3-month visit period = (365.25/12) * 3 ≈ 92 days

Table 4: Visit Time Windows for Seizure Diary

Period	Visit Period	Scheduled Visit Day	Window*
Treatment Year 1	Month 0 – 3	Day 1 – Day 92	Days ≤ 1 – Study Day of Month 3 visit
	Month 4 – 6	Day 93 – Day 184	Study day of Month 3 visit + 1 – Study day of Month 6 visit
	Month 7 – 9	Day 185 – Day 276	Study day of Month 6 visit + 1 – Study day of Month 9 visit
	Month 10 – 12	Day 277 – Day 368	Study day of Month 9 visit + 1 – Study day of Month 12 visit
Treatment Year 2 - 3	Month 13 – 18	Day 369 – Day 552	Study day of Month 12 visit + 1 – Study day of Month 18 visit
	Month 19 – 24	Day 553 – Day 736	Study day of Month 18 visit + 1 – Study day of Month 24 visit
	Month 25 – 30	Day 737 – Day 920	Study day of Month 24 visit + 1 – Study day of Month 30 visit
	Month 31 – 36	Day 921 – Day 1104	Study day of Month 30 visit + 1 – Study day of Month 36 visit

*refer to Table 3 for visit window of each visit time point.
Study Day is calculated as (visit date – date of the first dose in UX007G-CL202 study + 1), if visit date is on or after the date of the first dose in UX007G-CL202 study; and as (visit date – date of the first dose), if visit date is before the date of the first dose in UX007G-CL202 study.

7.3 Testing/Validation Plan

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

7.4 Software

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

8 STATISTICAL METHODS OF ANALYSES

8.1 General Principles

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

8.2 Subject Accountability

The number and percentage of subjects in the Full Analysis Set, Full Analysis Set – SF-10 and Full Analysis Set – SF-12v2 will be summarized by subject group and subject seizure type. Subjects excluded from the analysis sets will be listed. The number and percentage of subjects who complete the study, and who prematurely discontinue will be presented.
The reasons for premature discontinuation from treatment as recorded on CRFs will be summarized as well.

8.3 Protocol Deviations

Protocol deviations will be summarized for the Full Analysis Set. Both major and minor protocol deviations will be listed.

8.4 Demographic and Baseline Characteristics

For all subjects, age at informed consent in UX007G-CL202 study will be presented.
Other demographic parameters (e.g., gender, race, ethnicity and age at Glut1 DS diagnosis) and other baseline characteristics measured at baseline of the feeder study will be used for Rollover subjects. For Non-Rollover subjects, demographic and other baseline characteristics measured at the baseline of UX007G-CL202 study will be used.

8.5 Disease Characteristics and Medical History

Summary statistics will be presented for the Full Analysis Set, for the following parameters:

- Duration of Glut1 DS symptom
- Glut1 DS mutation description
- Glut1 DS symptoms history including whether ongoing
- Ketogenic Diet (KD) history and reason for KD discontinuation
- Seizure history by type
- Average number of observable seizures per month over the last 6 months

For Rollover subjects, medical history recorded at the baseline of the UX007G-CL201 study and the current study will be used. For Non-Rollover subjects, medical history recorded at in the current study will be used.

8.6 Prior and Concomitant Medication

For Rollover subjects, prior medication will be defined as any medication taken before the first dose in the UX007G-CL201 study. For Non-Rollover subjects, prior medication will be defined as any medication taken prior to the first dose of UX007 in the current study.

Concomitant medication is defined as any medication taken during the study between the day of the first dose of the investigational product and the day of the last dose of the investigational product in UX007G-CL202 study. 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. The number and proportion of subjects receiving each reported prior and concomitant medication will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term for the Full Analysis Set. Multiple uses by a subject of the same drug will be counted only once in the summary tables.

8.7 Investigational Product Administration

8.7.1 Extent of Exposure

Exposure duration to UX007 will be summarized for the Full Analysis Set.

8.7.2 Measurement of Treatment Compliance

Number of days during a visit period is calculated as (end of visit period date – start of visit period date + 1). Percent of days missed for a period is 100×(number of days during the visit period with dose non-compliance)/(number of days during the period). Descriptive statistics for dosing compliance will be summarized. Number and percent of days with missing dose will also be summarized.

8.7.3 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

8.8 Efficacy Analysis

Because the primary objective of this study is to evaluate the long-term safety, the efficacy parameters will not be grouped into primary or secondary categories. Efficacy analyses will be based on the Full Analysis Set.

- Seizure frequency

For Rollover subjects, frequency of seizures (normalized to a 4-week rate) up to first year will be analyzed using generalized estimating equations (GEE), with reduction from baseline for each visit period (see Section 7.2.5, Table 4) as the response variable, baseline as covariates, visit period (in UX007G-CL202 study) as a factor, identity link function and exchangeable within subject working correlation matrix.

Frequency of seizures will be derived for each subject based on subject seizure type. Observable seizures from the diary will be used for Observable Seizures Subjects. For Absence Seizures Only Subject, the absence EEG data measured at the scheduled visit (matching the each period end time specified for seizure diary, see Section 7.2.5, Table 4) will be used, e.g., scheduled Month 3 EEG absence seizure data will be used to assess seizure frequency for visit period Month 0 – 3.

For Non-Rollover subjects, descriptive statistics of observed value will be presented.

- Seizure frequency from diary

For Rollover subjects, observed value and reduction from baseline in frequency of observable seizure and absence seizure (normalized to a 4-week rate) for each visit time period (see Section 7.2.5, Table 4) will be summarized by subject group and subject seizure types.
For Non-Rollover subjects, descriptive statistics of observed value will be presented.

- Seizure frequency from EEG

For Rollover subjects, observed value and reduction from baseline in frequency of absence seizure and non-absence seizure (normalized to a 24-hour rate) for each visit time point (see Section 7.2.5, Table 4) will be summarized by subject group and subject seizure types.
For Non-Rollover subjects, descriptive statistics of observed value will be presented.

For Rollover subjects, descriptive statistics for observed value and change from baseline will be presented by assessment time point for the following endpoints:

- CNS total score
- SF-10 summary scores
- SF-12 domain/summary score

For Non-Rollover subjects, descriptive statistics of observed value will be presented.

8.9 Safety Analysis

All safety analysis will be performed using the Full Analysis Set. No statistical comparisons will be performed.

8.9.1 Adverse Events

The latest Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a system organ class (SOC) and preferred term.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose in this study, and was not present prior to the first dose in this study, or it was present at the first dose in this study but increased in severity during the study.

Subject incidence of TEAEs will be tabulated by SOC and preferred term. Serious TEAEs, treatment-related TEAEs, grade 3/4 TEAEs, fatal TEAEs, TEAEs leading to study discontinuation, and TEAEs leading to treatment discontinuation will be summarized. Gastrointestinal TEAE will also be summarized.

Detailed listings for all AEs, SAEs, treatment related TEAEs, treatment related SAEs, AEs leading to the discontinuation, and death will also be generated. The severity will be based on Common Terminology Criteria for Adverse Events (CTCAE). If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = Death related to AE.

8.9.2 Laboratory Parameters

Clinical laboratory values (in SI units) at each assessment time point will be summarized for laboratory parameters in hematology, chemistry and urinalysis. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside of reference ranges) and/or clinically significant abnormalities after study drug administration will be presented by laboratory measurement.

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)

Hy's Law criteria will be applied against test results. Subjects with serum total bilirubin >2 x ULN and ALT or AST >3 x ULN will be considered positive for Hy's law status. Results will be presented in shift tables. For Hy's Law, shift tables will be produced:

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

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

8.9.3 Vital Signs

The following vital signs and weight will be summarized by time point.

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

8.9.4 Physical Examination

Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Physical examination abnormality findings will be listed over time by subject.

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. 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 visit in the summary.

8.9.6 PK Analyses

Plasma levels of UX007 metabolites will be summarized using descriptive statistics.

9 REFERENCES

Not applicable.

10 APPENDICES

10.1 Appendix A. Efficacy Endpoint Summary Table

Endpoint	Statistical Method	Analysis Population
Reduction from baseline in frequency of seizures up to first year	GEE	FAS (Rollover subjects)
Frequency of seizures	Descriptive statistics	FAS (Rollover subjects)
Frequency of seizures	Descriptive statistics	FAS (Non-Rollover subjects)
Frequency of observable/absence seizures by seizure diary	Descriptive statistics	FAS
Frequency of absence/non-absence seizures by EEG	Descriptive statistics	FAS
CNS total score	Descriptive statistics	FAS
SF-10 summary scores	Descriptive statistics	FAS – SF10
SF-12 domain/summary score	Descriptive statistics	FAS – SF12v2

10.2 Appendix B. Schedule of Events

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

[*]Refer to the Study Reference Manual for a recommended schedule of the assessments during the 1-day and 2-day visits. The Investigator may use clinical judgment in deciding whether to administer certain assessments to subjects based on age, development, and cognitive ability, as appropriate. The SF-10/SF-12v2

will not be performed if no pre-treatment baseline is available from feeder study (e.g. subjects entering from ISTs or subjects from UX007G-CL201 or other Ultragenyx-sponsored clinical studies who were too young or compromised at pre-treatment Baseline).

[1] The Baseline Visit may occur in conjunction with the last scheduled visit from study UX007G-CL201 to avoid duplication of assessments. If the time elapsed between the last UX007G-CL201 study visit and the Baseline Visit for this study is > 1 month, the full panel of Baseline Visit assessments must be completed. Subjects will return to the clinic at 3-month intervals during Treatment Extension Year 1 (± 1 week), and 6-month intervals during Years 2 and 3 (± 2 weeks). Reporting of adverse events and concomitant medications at Months 15, 21, 27, and 33 will be completed via telephone call (TC) or optional study site visit; visits to the study site at these time points are not required and are optional at the subject's discretion.

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

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

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

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

[6] Blood samples for UX007 metabolites will be drawn approximately 90 min following consumption of food and study drug.

[7] Vital sign measurements consist of seated systolic/diastolic blood pressure (millimeters of mercury), heart rate (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Vitals to be obtained at the beginning of each visit before any additional assessments are completed.

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

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

[10] The Columbia Suicide Severity Rating Scale (C-SSRS) baseline questionnaire will be administered on the initial visit; the Since Last Visit questionnaire will be administered at all subsequent visits.

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

[12] A subject may have been off UX007 treatment prior to enrollment; in these cases, UX007 may be titrated per discretion of the investigator. Study drug dispensation is not required at the Months 15, 21, 27, or 33 but may be dispensed to subjects who opt to return to the study sites for these visits.

[13] Refer to Pharmacy Manual for instructions on return of empty and opened study drug bottles. Treatment compliance and accountability will only be evaluated at Months 15, 21, 27, and 33 for those subjects who opt to return to the study sites for these visits.

[14] Safety Follow-up Phone Call to be conducted 30-35 days after last dose of study drug. The last subject's Safety Follow-up Phone Call is the End-of-study Time Point. The site personnel will initiate this safety follow-up telephone call to collect information on any ongoing or new AEs, serious adverse events (SAEs), and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.

10.3 Appendix C. Gastrointestinal Standardized MedDRA Query

The following MedDRA PTs are included in the gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ) version 17.1. Analyses will be performed based on the SMQ of the MedDRA version corresponding to the data snapshot / database lock.

Narrow Scope	Broad Scope
Abdominal discomfort	Anorectal swelling
Abdominal distension	Antacid therapy
Abdominal pain	Antidiarrhoeal supportive care
Abdominal pain lower	Antiemetic supportive care
Abdominal pain upper	Breath odour
Abdominal symptom	Chest pain
Abdominal tenderness	Colonic lavage
Abnormal faeces	Dysphagia
Aerophagia	Early satiety
Anorectal discomfort	Gastritis prophylaxis
Bowel movement irregularity	Gastrointestinal disorder therapy
Change of bowel habit	Gastrointestinal tract irritation
Constipation	Gastrooesophageal reflux prophylaxis
Defaecation urgency	Glycogenic acanthosis
Diarrhoea	Hypovolaemia
Epigastric discomfort	Laxative supportive care
Eructation	Malabsorption
Faecal volume decreased	Mucous stools
Faecal volume increased	Oesophageal polymer implantation
Faeces hard	Pernicious anaemia
Faeces soft	Post procedural constipation
Flatulence	Post procedural diarrhea
Frequent bowel movements	Post-tussive vomiting
Gastrointestinal pain	Probiotic therapy
Gastrointestinal sounds abnormal	Procedural nausea
Gastrointestinal toxicity	Procedural vomiting
Infrequent bowel movements	Prophylaxis against diarrhoea
Nausea	Prophylaxis of nausea and vomiting
Non-cardiac chest pain	Regurgitation
Oesophageal discomfort	Retching
Oesophageal pain	Steatorrhoea
Premenstrual cramps	Vomiting projectile
Vomiting	