STATISTICAL ANALYSIS PLAN

Title:	**A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome**
Protocol:	**UX007G-CL201**
Investigational product:	**UX007 (triheptanoin)**
Phase:	**2**
Sponsor:	**Ultragenyx Pharmaceutical Inc.** **60 Leveroni Court** **Novato, CA, USA 94949**
Author:	PPD **Biostatistics**
Date:	**11 January 2017**
Version Number:	**2.0**

STATISTICAL ANALYSIS PLAN

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL201 Version 2.0

11 January 2017

The amended version of the Statistical Analysis Plan for UX007G-CL201 (Version 1.0, dated 17 October 2016) has been modified by Version 2.0 to clarify the primary endpoint and analysis. The major changes to the protocol are summarized below; additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Added language to the primary efficacy endpoint (Section 4.1) stating that the endpoint derivation depends on the subject seizure type at randomization.

   Rationale: This change was made for clarity.

2. Revised Section 5.6 on classification of subjects at randomization by seizure type to clarify purpose of classification and that all subjects are either an observable seizures subject, an absence seizures subject, or both.

   Rationale: This change was made for clarity.

3. Added Unknown (UNK) type to diary seizures classification (Section 5.7.5).

4. Added language to the primary efficacy analysis (Section 8.6.3) stating that sensitivity analyses assessing the impact of missing data will be performed.

   Rationale: This change was made for clarity.

5. Added Appendix D with SAS code for the primary statistical analysis.

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LIST OF ABBREVIATIONS

6MWT	6-Minute Walk Test
AE	Adverse Event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Beery-VMI	Beery-Buktenica Developmental Test of Visual Motor Integration
BHB	beta-hydroxybutyrate
BHP	beta-hydroxypentanoic acid
BUN	blood urea nitrogen
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity scale
CNS	Columbia Neurological Score
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	electronic data capture
EEG	electroencephalogram
FDA	Food and Drug Administration (United States)
GEE	Generalized Estimating Equation (statistical model)
GGT	gamma glutamyl transpeptidase
GI	Gastrointestinal
Glut1	glucose transporter type 1
Glut1 DS	glucose transporter type 1 deficiency syndrome
GMFM-88	Gross Motor Function Measure-88
KD	ketogenic diet
L	Litre
LSM	Least Square Mean
MCS	Mental Component Summary Scale
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PAL	Paired Associates Learning Test
PCS	Physical Component Summary Scale
PED	paroxysmal exertional dyskinesia
PEDI-CAT	Pediatric Evaluation of Disability Inventory Computer Adaptive Test

PHS-10	physical summary score
PK	Pharmacokinetics
PPVT	Peabody Picture Vocabulary Test
PSS-10	psychosocial summary score
PT	Preferred Term
RBC	red blood cell
RCPM	Raven's Coloured Progressive Matrices
RTI	Reaction Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-10	Short Form 10 Health Survey for Children
SF-12v2	(Medical Outcomes Study) 12-Item Short Form – version 2
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SSP	Spatial Span
SWM	Spatial Working Memory
TEAE	Treatment-Emergent Adverse Event
UX007	Investigational Product/study drug, triheptanoin
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

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-CL201 original protocol and all amendments through Amendment 4 dated 30 November 2015. The data collected in this study will evaluate the safety and efficacy of UX007 in subjects with glucose transporter type 1 deficiency syndrome. The primary efficacy endpoint is the reduction from baseline to week 8 in frequency of seizures.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of the study are to:

- Evaluate the efficacy of UX007 compared to placebo as measured by the reduction from baseline to week 8 in frequency of seizures: observable generalized and partial-onset seizures measured by diary for 6 weeks prior to randomization and after 2-week titration until Week 8, and absence seizures measured by overnight electroencephalography (EEG) at baseline and Week 8
- Evaluate the safety of UX007 via adverse event (AE) rates, laboratory values, and electrocardiogram (ECG)

2.2 Secondary Objectives

The secondary objectives of the study are to:

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

2.3 Exploratory Objectives

Exploratory objectives are to:

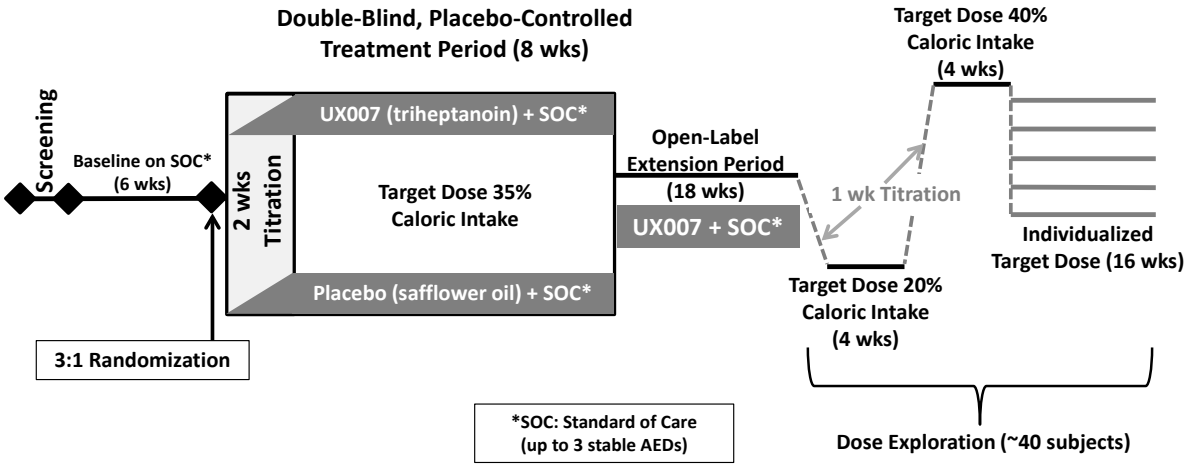
- Evaluate the effects of UX007, from baseline through Weeks 8 and 52 on:
  - Neurological function using the Columbia Neurological Score (CNS)

  - Physician global impression of change in clinical status using the Clinical Global Impression - Severity scale (CGI-S) and Clinical Global Impression - Improvement scale (CGI-I)
  - Receptive vocabulary using the Peabody Picture Vocabulary Test (PPVT) (assessed at select sites)
  - Subject or caregiver-reported quality of life using Short Form-10™ (SF-10) Health Survey for Children or SF-12 for adults
  - PK properties of UX007 and its metabolites
- Evaluate the effects of UX007, from baseline through Weeks 8 and 52 on (assessed at select sites):
  - Functional disability by caregiver report using the Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT)
  - Gait, using gait analysis by computerized mat
  - Visual motor integration using the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery-VMI)
  - Spatial understanding and abstract reasoning using the Raven's Coloured Progressive Matrices (RCPM)

3 STUDY DESIGN

UX007G-CL201 is a randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of UX007 in Glut1 DS. Figure 1 provides a schematic of the study design. As background for the statistical methods presented in the SAP, this section provides an overview of the study design. This overview is a summary only. The protocol is the definitive reference for all matters discussed in what follows.

Figure 1: UX007G-CL201 Study Schema



3.1 Study Population

The study will enroll approximately 40 pediatric, adolescent, and adult subjects who are currently not on, or not fully compliant with a ketogenic or other prescribed high-fat diet. Enrolled subjects are otherwise able to maintain standard of care treatment with up to 3 antiepileptic drugs (AEDs) throughout the duration of the study.

3.2 Dosage and Administration

Dosing will be initiated using a 2-week titration schedule until the subject has reached the target of 35% of total daily calories from study drug (~1-4 g/kg/day depending on age). If a subject has not reached the target of 35% of total daily calories by the end of the 2-week titration period, dose titration should continue until the maximum tolerated dose is reached. After an 8-week double-blind Treatment Period, the open-label Extension Period will begin, wherein all subjects will be treated with UX007 through Week 52 of the study.
Following the Week 26 visit, all 40 subjects will participate in a 10-week Dose Exploration Period. The dose will be titrated over 1 week down to 20% of total daily caloric intake. If there are breakthrough seizures during the down titration period, or in the opinion of the investigator there has been a worsening of symptoms prior to completion of the 4-week period, the subject may begin the up-titration phase early. After 4 weeks at the 20% dose level, the UX007 dose will then be titrated up over 1 week to 40% of total daily caloric

intake and maintained at that level for 4 weeks. If a subject cannot tolerate titrating up to the 40% dose level, the dose should be titrated to the maximum tolerated dose as determined by the Investigator. After 4 weeks at the 40% (or maximum tolerated) dose level, the subject will continue in the open-label Extension period, and maintained on a UX007 dose to be determined by the Investigator.

A complete schedule of events specific for each period of the study is found in the protocol (Section 2, Table 2.1) and repeated herein as Appendix B.

3.3 Blinding and Randomization Methods

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. Subjects will be assigned to investigational product or placebo treatment groups via manual randomization based on a manual randomization process developed by the Sponsor. Randomization will seek to stratify subjects based on seizure frequency reported during the 6-week baseline period. At the end of the Baseline Period, eligible subjects will be randomized in a 3:1 ratio to either UX007 or placebo. Note that the first 3 subjects PPD were randomized in a 1:1 ratio because they were randomized prior to the implementation of Protocol Amendment 3.

The titration and Treatment Period (Weeks 0-8) will be conducted as a randomized, double-blind, placebo-controlled study. Double-blind conditions will be established so that neither the sponsor, subject or site personnel involved in study conduct will know the identity of a subject's treatment. Following completion of the double-blind period, all eligible subjects will receive open-label UX007 for a 44-week open-label Extension Period (Weeks 9-52) to assess long-term safety and duration of effect.

3.4 Stratification Factors

Randomization is stratified based on baseline seizure frequency of ≤ 8 vs. > 8 seizures per 4 weeks based on the seizure diary for approximately 6 weeks between the screening and randomization visits.

3.5 Sample Size Considerations

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

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

3.6 Primary Analyses

Evaluations will occur at the following key time points:

- Primary Analysis: The primary, week 8, analysis will occur when all subjects have completed the 8 week double-blind placebo-controlled treatment period, or withdrawn from the study prior to the week 8 visit.
- Final Analysis: The final analysis will occur when all subjects have completed the open-label extension period, or withdrawn from the study.

3.7 Data Monitoring Committee

A DMC with appropriate expertise in the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial.
The DMC will also monitor individual subject tolerability and implement individual subject stopping criteria based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. The DMC will be consulted for the management of individual subjects who experience unacceptable tolerability issues (such as significant gastrointestinal distress). The DMC may:

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

The detailed roles and responsibilities of the DMC are specified in the DMC Charter.

4 STUDY ENDPOINTS, COVARIATES AND SUBGROUPS

The clinical efficacy tests / instruments evaluated in this study are summarized in Table 1. See the study protocol for the detailed description of each test.

Table 1: Study Outcomes

Seizure Frequency and Response

- Observable seizures measured by seizure diary [**]
- Absence seizures measured by overnight electroencephalogram (EEG) [**]

Movement

- Movement ability measured by 6-minute Walk Test (6MWT) [*]
- Paroxysmal exertional dyskinesia (PED) events measured by 6MWT [*]
- Gross motor function measured by Gross Motor Function Measure-88 (GMFM 88) [*][#]
- Gait analysis measured during 6MWT [#]

Neurological Function

- Neuropsychological function measured by Computerized Neuropsychological Test - Cambridge Neuropsychological Test Automated Battery (CANTAB) [*]
- Physical neurological findings measured by Columbia Neurological Score (CNS)
- Global impression of disease improvement measured by Clinical Global Impression –Improvement (CGI-I)
- Receptive vocabulary achievement and verbal ability measured by Peabody Picture Vocabulary Test (PPVT) [#]
- Visual and motor coordination measured by Beery-Buktenica Developmental Test of Visual Motor Integration (Beery-VMI) [#]
- Spatial understanding and abstract reasoning measured by Raven's Coloured Progressive Matrices (RCPM) [#]

Quality of Life

- Physical and psychosocial health-related quality of life measured by Short Form-10 (SF-10) Health Survey in subjects under 18 years of age
- Physical and psychosocial health-related quality of life measured by Short Form-12 (SF-12) Health Survey in subjects 18 years of age and over
- Functional capabilities and performance measured by Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT)[#]

[**] Primary efficacy measures
[*] Secondary efficacy measures
[#] Measured at select sites only

Each of the primary and secondary endpoints will be compared between the UX007 and placebo groups during the double-blind, placebo-controlled treatment period.

4.1 Primary Efficacy Endpoint

The primary endpoint to evaluate the efficacy of UX007 in Glut1 DS is as follows:

- Reduction from baseline to week 8 in frequency of seizures (normalized to a 4-week rate): observable seizures measured for 6 weeks after 2-week titration by diary and absence seizures measured overnight by electroencephalography (EEG). The primary efficacy endpoint will be derived for each subject based on subject seizure type at randomization: observable seizures from the diary will be used for Observable Seizures Subjects and absence seizures from EEG will be used for Absence Seizures Only Subjects (see Section 5.6).

4.2 Secondary Efficacy Endpoints

The following are considered secondary endpoints to evaluate the efficacy of UX007 in Glut1 DS:

- Reduction from baseline to week 8 in frequency of observable seizures (normalized to a 4-week rate) measured for 6 weeks after 2-week titration by diary
- Reduction from baseline to week 8 in frequency of absence seizures (normalized to a 4-week rate) measured overnight by EEG
- Seizure response at Week 8, defined as at least 50% reduction from baseline to week 8 in frequency of seizures
- Observable seizure response at Week 8, defined as at least 50% reduction from baseline to week 8 in frequency of observable seizures measured by diary
- Absence seizure response at Week 8, defined as at least 50% reduction from baseline to week 8 in frequency of absence seizures measured overnight by EEG
- Cognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB): change from baseline to Week 8 in the following scores:
  - Reaction Time (RTI):
    - Simple Choice Median Reaction Time (RTIMDSRT)
    - Five Choice Median Reaction Time (RTIMDFRT)
    - Simple Choice Standard Deviation (RTISRTSD)
  - Spatial Span (SSP):
    - Span Length (SSPSLF)
  - Paired Associates Learning (PAL):
    - Total Errors (Adjusted) (PALTEA)
    - First Trial Memory Score (PALFTMS)

  - Spatial Working Memory (SWM):
    - Between Errors (SWMBE48)
    - Strategy (SWMS68)

- Change from baseline to Week 8 in distance traveled (in meters) as measured by 6MWT
- Change from baseline to Week 8 in distance traveled (in percent predicted) as measured by 6MWT
- Time (in minutes) to onset of paroxysmal exertional dyskinesia (PED) as measured during 6MWT through Week 8
- Gross motor function using the Gross Motor Function Measure-88 (GMFM-88): change from baseline to Week 8 in Total Score.
- Reduction from baseline over time in frequency of seizures (normalized to a 4-week rate): observable seizures measured daily by diary and absence seizures measured overnight by electroencephalography (EEG)
- Reduction from baseline over time in frequency of observable seizures (normalized to a 4-week rate) measured daily by diary
- Reduction from baseline over time in frequency of absence seizures (normalized to a 4-week rate) measured overnight by EEG

4.3 Exploratory Efficacy Endpoints

The following are considered exploratory endpoints and provide supplemental information to evaluate the efficacy of UX007 in Glut1 DS:

- Cognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB), change from baseline over time in the following scores: RTIMDSRT, RTIMDFRT, RTISRTSD, SSPSLF, PALTEA, PALFTMS, SWMBE48, SWMS68
- Change from baseline over time in distance traveled (in meters) as measured by 6MWT
- Change from baseline over time in distance traveled (in percent predicted) as measured by 6MWT
- Time (in minutes) to onset of paroxysmal exertional dyskinesia (PED) as measured during 6MWT over time
- Gross motor function using the Gross Motor Function Measure-88 (GMFM-88): change from baseline over time in the following scores: Lying and Rolling; Sitting; Crawling and Kneeling; Standing; Walking, Running and Jumping; Total Score
- Change from baseline in Neurological function using the Columbia Neurological Score (CNS) total score
- Physician global impression of change in clinical status (Guy 1976)

  - Clinical Global Impression - Improvement scale (CGI-I)
- Change from baseline in Receptive vocabulary using the Peabody Picture Vocabulary Test (PPVT) standardized score
- Subject or caregiver-reported quality of life using Short Form-10™ (SF-10) Health Survey for children (subjects 5 through 17 years of age): change from baseline in two component summary T-scores:
  - Physical Summary Score (PHS-10)
  - Psychosocial Summary Score (PSS-10)
- Subject or caregiver-reported quality of life using Short Form-12v2 (SF-12v2) Health Survey for adults (subjects 18 years of age and older): change from baseline in 8 domain norm based scores and two component T-scores:
  - Physical Functioning (PF)
  - Role Limitations due to Physical Health (RP)
  - Bodily Pain (BP)
  - General Health Perceptions (GH)
  - Vitality (VT)
  - Social Functioning (SF)
  - Role Limitations due to Emotions Problems (RE)
  - Mental Health (MH)
  - Physical Component Summary Scale (PCS-12)
  - Mental Component Summary Scale (MCS-12)
- Functional disability by caregiver report using the Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT) for all subjects under the age of 18 (or for subjects 18- 20 years as clinically indicated) at the time of informed consent: change from baseline in domain scale scores and T-scores
  - Daily Activities
  - Mobility
  - Social/Cognitive
  - Responsibility
- Gait, using gait analysis by computerized mat during 6MWT: change from baseline in the following measures:
  - Stride Length
  - Base of Support

  - Double Support
  - Velocity
  - Cadence
- Visual motor integration using the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery-VMI) for subjects between 2 and 18 years of age: change from baseline.
- Spatial understanding and abstract reasoning using the Raven's Coloured Progressive Matrices (RCPM): change from baseline in total score

4.4 Safety Endpoints

The following endpoints will be used to evaluate the safety of UX007:

- Treatment emergent adverse events (TEAEs) including treatment emergent serious adverse events (TESAEs), fatal AEs, TEAEs leading to discontinuation, treatment related TEAEs and treatment related TESAEs
- Gastrointestinal (GI) TEAEs categorized using the standardized MedDRA query (SMQ) as listed in Appendix C
- Clinically significant changes from baseline in the following:
  - Vital signs and weight
  - Physical examination and ECG findings
  - Clinical laboratory evaluations
  - Pregnancy testing/pregnancy of partner
  - Suicidal ideation and behavior assessments
  - Concomitant medications
- Drug concentration measurements and bioassays
  - Plasma peak levels of UX007
  - Plasma levels of UX007 metabolites: C4 ketone (BHB), C5 ketones (beta-hydroxypentanoate [BHP]), and heptanoate
  - Non-fasting BHB
  - Trough UX007 and metabolites

4.5 Covariates

Covariates that may be incorporated into models include an appropriate associated baseline value and an indicator for whether a subject is an Absence Seizures Only Subject. Transformations will be considered for model covariates that are overly skewed.

4.6 Subgroups

Subgroup analyses will be done based on the derived seizure variables at baseline (see Section 5.6).

5 DEFINITIONS

5.1 Baseline

Baseline observable seizure frequency (see Section 5.7.1) from the seizure diary will be derived by measuring over approximately 6 weeks between the screening visit and the day prior to the randomization visit.

For all other measures, baseline value will be the last non-missing assessment prior to or on the date of the first dose of investigational product.

The baseline value will be used for all analyses of changes from the randomization visit and the phrases "change from baseline" and "change from randomization" will be used interchangeably.

5.2 Duration of Investigational Product Exposure

For each subject, the duration of investigational product exposure is defined for a given study period as the date of last dose of study drug during the study period – date of first dose of study drug during the study period + 1.

For each subject, the duration of UX007 exposure is defined for a given study period as the date of last dose of UX007 during the study period – date of first dose of UX007 during the study period + 1.

5.3 Study Day

Study day is calculated as (visit date – date of the first dose of investigational product + 1) if the date is on or after the first dose of investigational product; or (visit date – date of the first dose of investigational product) if the date is prior the first dose of investigational product.

5.4 Dosing Compliance

Number of days during a period is calculated as (end of period date – first dose date + 1) for the titration and treatment periods, and (end of period date – week 8 visit date + 1) for the extension period. Percent of days missed for a period is 100×(number of days during the period with dose non-compliance)/(number of days during the period).

5.5 Change from Baseline and Percent Change from Baseline

Generally, for measurements at any timepoint T after baseline, change from baseline is defined as

$$\text{Change from Baseline at } T = \text{Measurement at } T - \text{Measurement at Baseline}$$

Percent change from baseline at T is defined as

$$\text{Percent Change from Baseline at } T = 100 \times \frac{\text{Measurement at } T - \text{Measurement at Baseline}}{\text{Measurement at Baseline}}$$

5.6 Classification of Subjects at Randomization by Seizure Type

Classification of subjects is used to derive the primary efficacy endpoint and to define which subjects are included in secondary endpoint analyses of specific seizure types. At the Randomization Visit, subjects can be classified according to the types of seizures that are recorded on the diary as follows:

- 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 5.7.5) greater than or equal to 4 at Randomization
  - Observable Seizure Frequency less than 4 at Randomization and Absence Seizure Frequency less than 4 at Randomization
- Absence Seizures Subject: a subject who meets any of the following:
  - has seizure types M, N, O or P (see Section 5.7.5) recorded on the seizure diary during the Baseline Period
  - has absence seizures documented on the Screening EEG
  - Absence Seizure Frequency (see Section 5.7.2) greater than 0 at Randomization

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 randomized 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

5.7 Derived Seizure Efficacy Variables

5.7.1 Observable Seizure Frequency

Observable seizure frequency, the observable non-absence seizure frequency from the diary (normalized to a 4-week rate), is defined as

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

See Section 5.7.5 for the list of observable seizure types that are counted. For analyses, observable seizure frequency will be defined at each of the following timepoints as follows:

- Baseline: approximately 6 weeks between the day of the screening visit and the day prior to the randomization visit
- End of Titration: approximately 2 weeks between the day of the randomization visit and the day prior to the end of titration visit
- Week 8: approximately 6 weeks between the day of the end of titration visit and the day prior to the week 8 visit

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 weeks 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.

5.7.2 Absence Seizure Frequency

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

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

See Section 5.7.6 for the list of absence seizure types that are counted. Absence seizure frequency at baseline is measured at the randomization visit. Absence seizure frequency at 8 weeks is measured at the week 8 visit (Visit 5).

5.7.3 Percent Reduction from Baseline in Seizure Frequency

For observable or absence seizures, the percent reduction from baseline in seizure frequency during a period T is defined as

$$\text{Percent Reduction from Baseline} = 100 \times \frac{\text{Frequency at Baseline} - \text{Frequency at } T}{\text{Frequency at Baseline}}$$

The maximum percent reduction is 100% and occurs when the frequency is reduced to zero. If the frequency increases then the percent reduction is a negative number.

5.7.4 Seizure Response

Seizure response is defined as a percent reduction from baseline in seizure frequency greater than or equal to 50%.

Observable seizure response, at least 50% reduction from baseline in frequency of observable seizures measured by diary, is defined as percent reduction in observable seizure frequency greater than or equal to 50%.

Absence seizure response, at least 50% reduction from baseline in frequency of absence seizures measured overnight by EEG, is defined as percent reduction in absence seizure frequency greater than or equal to 50%.

5.7.5 Classification of Seizures from Diary

Table 2 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 2: Seizure Classification by Diary

Seizure Code (Diary)	Seizure Classification	Counted Towards Inclusion Criteria	Counted as Observable 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 [*]	
N	Atypical Absence	X [*]	
O	Absence with Special Features (Myoclonic absence)	X [*]	
P	Absence with Special Features (Eyelid myoclonia)	X [*]	

Seizure Code (Diary)	Seizure Classification	Counted Towards Inclusion Criteria	Counted as Observable Seizure
Q	Unclassified (Inc. epileptic spasms)		
UNK	Unknown		

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

5.7.6 Classification of Seizures from EEG

Table 3 shows the seizure classifications that are distinguished in the EEG and which are counted when deriving absence seizures endpoints.

Table 3: Seizure Classification by EEG

Label	Definition	Absence Seizure
GenTC-BMS	Generalized Tonic-Clonic	
GenT-BMS	Generalized Tonic	
GenC-BMS	Generalized Clonic	
Partial-BMS	Partial	
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	

5.8 Other Derived Efficacy Variables

5.8.1 Cambridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB scores are shown in Table 4. The Motor Screening Test (MOT) is only used to evaluate whether the subject is eligible to continue with the remaining tests.

Table 4: CANTAB Scores

Cognitive Domain	Specification	Sense	Form	Range
Attention	RTI Simple choice reaction time standard deviation (RTISRTSD)	Lower is better	Continuous	0-5000
Reaction Time	RTI median simple choice reaction time (RTIMDSRT)	Lower is better	Continuous	100-5100 (ms)
Reaction Time	RTI median 5-choice reaction time (RTIMDFRT)	Lower is better	Continuous	100-5100 (ms)
Episodic memory/ new learning	PAL total errors adjusted (PALTEA)	Lower is better	Discrete ordinal	0-137
Episodic memory	PAL first trial memory score (PALFTMS)	Higher is better	Discrete ordinal	0-27
Sequential memory	SSP Span Length (SSPSLF)	Higher is better	Discrete ordinal	2-9
Working Memory	SWM between errors (SWMBE48)	Lower is better	Discrete ordinal	0-360
Executive function/ strategy	SWM strategy (SWMS68)	Lower is better	Discrete ordinal	4-28

5.8.2 Percent predicted 6MWT distance

The percent predicted 6MWT formula which is applicable at enrollment will be used for that subject throughout the study.

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

For males:

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

and for females:

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

where X_i is the percent predicted 6MWT result at time i for subject X, and X_{0i} is the 6MWT result (in meters) at time i for subject X. Height and age at the study visit will be used for the calculation for the duration of the study. If height is missing at the study visit then the nearest available measurement will be used. If there are no height measurements then percent predicted will not be calculated.

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

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

where X_i is the percent predicted 6MWT result at time i for subject X, X_{0i} is the 6MWT result (in meters) at time i for subject X, and $Gender$ is equal to 0 if the subject is male or 1 if the subject is female. Height at baseline will be used for calculation for the duration of the study, and age at the study visit will be used for the calculation for the duration of the study.
If height is missing then the nearest available measurement will be used.

5.8.3 Gross Motor Function Measure-88 (GMFM-88)

The GMFM-88 scores include the following:

- Lying & Rolling Score, Range 0–100%, Higher is better
- Sitting Score, Range 0–100%, Higher is better
- Crawling & Kneeling Score, Range 0–100%, Higher is better
- Standing Score, Range 0–100%, Higher is better
- Walking, Running & Jumping Score, Range 0–100%, Higher is better
- Total Score = (Sum of 5 Above Scores) / 5, Range 0–100%, Higher is better

5.8.4 Columbia Neurological Score (CNS) total score

The CNS is a quantitative tool developed to summarize neurological exam findings (Kaufmann et al. 2004). The Columbia Neurologic Score (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.

5.8.5 Peabody Picture Vocabulary Test (PPVT) standardized score

The PPVT is a test of receptive vocabulary achievement and verbal ability that is normed for children as young as 2 years of age (Dunn et al. 2007). The PPVT results in the following scores:

- Raw Score [PPVTRAW], Range 0–228, higher is better

- Standard Score [PPVSTSCR], Range 20–160, higher is better
- 95% Confidence Interval-Upper [PPVCONUP], Range 20–166, higher is better
- 95% Confidence Interval-Lower [PPVCONLO], Range 14–154, higher is better
- Percentile Rank [PPVTPERC], Range <0.1 – >99.9, higher is better
- Age Equivalent [PPVTAGEQ], Range <2:0 – >24:11, higher is better
- Growth Scale Value (GSV) [PPVTGSV], Range 12–271, higher is better

5.8.6 SF-10 Health Survey

The SF-10 Health Survey is assessed for children 5 to 17 years of age. Two summary measures (the Physical Summary Score and the Psychosocial Summary Score) are calculated from raw scores to have a mean of 50 and SD of 10.

The T-score Based scoring (described in Section 5.8.7) is also 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). Although scale scores are standardized to a mean of 50 and a standard deviation of 10 in the combined U.S. general population and clinical samples, age-specific t-scoreative data should always be used for comparison purposes when results for individual children are being considered or when aggregate data are limited to a specific age range for which t scoreative data are available.

5.8.7 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. Additionally two summary component scores are calculated from domain scores (Physical Component Summary Scale [PCS] and the Mental Component Summary Scale [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 QualityMetric 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.

The main advantage of T-score Based scoring of the adult SF tools is easier interpretation. By using the T-score Based scoring method, your data are scored 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. Because the standard deviation for each scale is 10, it is easier to see exactly how far above or below the mean a score is in standard deviation units (10 points = 1 standard deviation unit).

5.8.8 Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT)

The Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) is a measure of functional capabilities and performance designed for use in children and youth from birth through 20 years of age with a variety of physical conditions (Haley et al. 2011). PEDI-CAT includes 4 domains (daily activities, mobility, social/cognitive and responsibility). Only 3 domain scores (daily activities, mobility, social/cognitive) will be included in the analysis for the subjects under 3 years of old. Each of the 4 PEDI CAT domains will be presented as Score, SE, T-Score and Percentile. Higher is better for Score, T-Score and Percentile. The assessment will be administered at select sites.

5.8.9 Gait, using gait analysis by computerized mat during the 6MWT

At select sites, the computerized mat may be used to assess gait during the 6MWT as the subject walks across the mat. The following gait assessments will be assessed at select sites:

- Stride Length (cm)
- Base of Support (cm)
- Double Support (% of gait cycle)
- Velocity (cm/sec)
- Cadence (steps/minute)

5.8.10 Beery-Buktenica Developmental Test of Visual Motor Integration (Beery-VMI)

The Beery-VMI measures the extent to which individuals can integrate their visual and motor abilities (Beery et al. 2004). The test is normed for children 2-18 years of age.
The Beery-VMI will be administered to subjects at select sites to obtain the following scores: Raw Score (Range 0–30, higher is better), Standard Score, Scaled Score, and Percentile.

5.8.11 Raven's Coloured Progressive Matrices (RCPM)

The RCPM is a test of spatial understanding and abstract reasoning developed for individuals 5 years of age and older (Raven et al. 1998). At select sites, the RCPM will be administered to all subjects, at the clinical judgment of the test administrator, to obtain Total Score (Range 0–60, higher is better) and Percentile.

6 ANALYSIS POPULATIONS

The following analysis sets are defined for this study.

6.1 Screened Population

The Screened Population will consist of all subjects who underwent a Screening Visit.

6.2 Randomized Population

The Randomized Population will consist of all subjects in the Screened Population who were randomized to a treatment group in the study.

6.3 Efficacy Analysis Set

The Efficacy Analysis Set includes all randomized subjects who received at least one dose of investigational product. For efficacy analyses, subjects are analyzed according to study treatment as randomized.

6.3.1 Efficacy Analysis Set – Observable Seizures

The Efficacy Analysis Set – Observable Seizures is the subset of subjects in the Efficacy Analysis Set who are Observable Seizures Subjects (see Section 5.6).

6.3.2 Efficacy Analysis Set – Absence Seizures

The Efficacy Analysis Set – Absence Seizures is the subset of subjects in the Efficacy Analysis Set who are Absence Seizures Subjects (see Section 5.6).

6.3.3 Efficacy Analysis Set – Observable Seizures Only

The Efficacy Analysis Set – Observable Seizures Only is the subset of subjects in the Efficacy Analysis Set who are Observable Seizures Only Subjects (see Section 5.6).

6.3.4 Efficacy Analysis Set – Absence Seizures Only

The Efficacy Analysis Set – Absence Seizures Only is the subset of subjects in the Efficacy Analysis Set who are Absence Seizures Only Subjects (includes some subjects with fewer than 4 observable seizures per 4 weeks, see Section 5.6).

6.3.5 Efficacy Analysis Set – CANTAB

The efficacy analysis set – CANTAB is the subset of subjects in the efficacy analysis set who had a baseline and at least one post baseline (Week 4 or Week 8) CANTAB assessment performed.

6.3.6 Efficacy Analysis Set – 6MWT

The efficacy analysis set – 6MWT is the subset of subjects in the efficacy analysis set who had a baseline and at least one post baseline (Week 4 or Week 8) 6MWT assessment performed.

6.3.7 Efficacy Analysis Set – GMFM-88

The efficacy analysis set – GMFM-88 is the subset of subjects in the efficacy analysis set who had a baseline and at least one post baseline (Week 4 or Week 8) GMFM-88 assessment performed.

6.3.8 Efficacy Analysis Set – CNS

The efficacy analysis set – CNS is the subset of subjects in the efficacy analysis set who had a baseline and Week 8 CNS assessment performed.

6.3.9 Efficacy Analysis Set – CGI-I

The efficacy analysis set – CGI-I is the subset of subjects in the efficacy analysis set who had CGI-I assessment performed at Week 8.

6.3.10 Efficacy Analysis Set – SF-10

The efficacy analysis set – SF-10 is the subset of subjects in the efficacy analysis set who had a baseline and Week 8 SF-10 assessment performed.

6.3.11 Efficacy Analysis Set – SF-12

The efficacy analysis set – SF-12 is the subset of subjects in the efficacy analysis set who had a baseline and Week 8 SF-12 assessment performed.

6.4 Per Protocol Analysis Set

The Per Protocol Analysis Set is the subset of subjects in the Efficacy Analysis Set who also meet the following criteria:

- met all inclusion and exclusion criteria at the time of randomization
- have ≥80% dosing compliance from baseline to week 8
- have sufficiently complete seizure data
  - Observable Seizures Subjects: completed at least 28 days of the seizure diary during the 6-week baseline period and again during weeks 3-8 of the double-blind placebo-controlled treatment period

- Absence Seizures Only Subjects: at least 8 hours evaluable EEG at randomization and again at week 8

6.4.1 Per Protocol Analysis Set – Observable Seizures

The Per Protocol Analysis Set – Observable Seizures is the subset of subjects in the Efficacy Analysis Set – Observable Seizures who met the following criteria:

- met all inclusion and exclusion criteria at the time of randomization
- have ≥80% dosing compliance from baseline to week 8
- have sufficiently complete seizure data: completed at least 28 days of the seizure diary during the 6-week baseline period and again during weeks 3-8 of the double-blind placebo-controlled treatment period

6.4.2 Per Protocol Analysis Set – Absence Seizures

The Per Protocol Analysis Set – Absence Seizures is the subset of subjects in the Efficacy Analysis Set – Absence Seizures who met the following criteria:

- met all inclusion and exclusion criteria at the time of randomization
- have ≥80% dosing compliance from baseline to week 8
- have sufficiently complete seizure data: at least 8 hours evaluable EEG at randomization and again at week 8

6.4.3 Per Protocol Analysis Set – CANTAB

The Efficacy Analysis Set – CANTAB is the subset of subjects in the Efficacy Analysis Set – CANTAB who met all inclusion and exclusion criteria at the time of randomization and have ≥80% dosing compliance from baseline to week 8.

6.5 Safety Analysis Set

The Safety Analysis Set includes all subjects who receive at least one dose of investigational product. For safety analyses during the double-blind period, subjects are summarized according to first study treatment actually received: either UX007 or placebo. Separate listings will capture actual dosing throughout.

6.6 Extension Analysis Set

The Extension Analysis Set is the subset of subjects in the Safety Analysis Set who continued after the 8 week double-blind placebo-controlled treatment period into the open-label extension period.

6.7 Pharmacokinetics Analysis Set

The Pharmacokinetics Analysis Set (PK Analysis Set) includes all subjects with available PK data.

7 DATA HANDLING AND ACCEPTANCE

7.1 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 a review of tables and listings for this study. Missing and incomplete data will be identified for investigation and possible resolution by Data Management prior to the study database lock.

Unless otherwise specified, for missing assessments for an individual subject, these data would remain as missing. When a change from baseline is assessed, only subjects with a baseline and at least one post baseline measurement will be included in the analysis.

For primary and secondary analyses related to reduction in seizures from baseline to Week 8, imputation will be used to enable inclusion in analyses of all subjects in the Efficacy Analysis Set, the Efficacy Analysis Set – Observable Seizures and the Efficacy Analysis Set – Absence Seizures.

- For observable seizures subjects who have incomplete diary data during the Baseline Period but at least one day complete, observable seizure frequency will be calculated by averaging over the days with complete diary data. The same rule will be used for the Double-Blind Placebo-Controlled Treatment Period. Note that this also applies to subjects who terminate early.
- For absence seizures subjects who have incomplete EEG at either Randomization or Week 8, absence seizure frequency will be calculated by averaging over the time that is complete, even if the EEG is not done overnight.
- For subjects who have completely missing data for either Randomization or Week 8, a reduction from baseline in the natural logarithm of seizure frequency (+ 1) value of zero will be imputed for the response variable in any analyses of reduction from baseline, and non-response will be imputed for the response variable in any analyses of seizure response. For subjects who have completely missing data for Randomization, the Week 8 value will be imputed if available for the baseline covariate; if both Randomization and Week 8 are missing then the average baseline value of the subjects with complete data in the same treatment group will be imputed for the baseline covariate. In additional analyses related to reduction in seizures, two alternate methods will be implemented:
    - the average reduction from baseline in the logarithm of seizure frequency (+ 1) of the subjects with complete data in the same treatment group will be imputed for the response variable in any analyses of reduction from baseline; and response will be imputed as yes if the imputed reduction from baseline is greater than or equal to the natural logarithm of 2 and no otherwise in any analyses of seizure response
    - no imputation, or complete case analysis – these data would remain as missing.

Imputation will not be used for analyses involving the open label period.

7.2 Missing Date Imputation Rules

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications.

1. Start Dates
    a. If the year is unknown, then the date will not be imputed and will be assigned a missing value.
    b. If the month is unknown, then:
        i. If the year matches the first dose date year, then impute the month and day of the first dose date.
        ii. Otherwise, assign "January."
    c. If the day is unknown, then:
        i. If the month and year match the first dose date month and year, then impute the day of the first dose date.
        ii. Otherwise, assign the first day of the month.
2. Stop Dates
    a. If the year is unknown, then the date will not be imputed and will be assigned a missing value.
    b. If the month is unknown, then assign "December."
    c. If the day is unknown, then assign the last day of the month.

7.3 Unscheduled or Early Termination Visits

In general, data collected by study visit will be summarized using the visit number specified in the database. Outcomes scheduled at a planned study visit but collected during an unscheduled visit or early termination visit will be mapped into the closest study visit based on the study day of the unscheduled visit or early termination visit, and the schedule of events in the protocol.

For outcomes where both the planned study visit and an unscheduled visit or early termination visit corresponding to that study visit are available, the planned study visit measurement will be used for the analysis.

All safety data including the planned study visits and unscheduled/early termination visits will be included in the shift tables.

All data will be included in the data listings and outcomes measured during unscheduled visits and early termination visits will be marked as acquired during an unscheduled visit.

Observable seizure frequency will be mapped to visits as described in Section 5.7.1.

7.4 Analysis Software

Data manipulation, tabulation of summary statistics, graphical representations and estimation of model parameters will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes. Scoring software from Cambridge Cognition (Cambridge, UK) will be used to score the CANTAB instrument described in Section 5.8.1. T-score Based scoring software from QualityMetric Inc. (Lincoln, RI) will be used to score the SF-12 and SF-10 Health Survey instruments described in Sections 5.8.6 and 5.8.7 respectively.

7.5 Coding of Events and Medications

Adverse events will be coded to standardize presentation of AEs and TEAEs. AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) system for reporting system organ classes and preferred terms.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

8 STATISTICAL METHODS OF ANALYSIS

8.1 General Principles

During the Double-Blind Placebo-Controlled Treatment Period, efficacy analyses will be based on the Efficacy Analysis Set or the Per Protocol Analysis Set. During the open label period, efficacy analyses will be based on the Extension Set. Safety analyses will be based on the Safety Analysis Set. Unless stated otherwise, statistical tests will be 1-sided hypothesis tests performed at the 5% level of significance and confidence intervals will be 2-sided 90% confidence intervals. 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.

Analyses and summaries by study period will be done for the following time periods:

- Double-blind placebo-controlled treatment period: after the date of the randomization visit until the date of the week 8 visit
- Open-label extension period: after the date of the week 8 visit until the date of the week 52 visit
- Dose exploration period: after the date of the week 26 visit until the date of the week 36 visit

Overall analyses and summaries will include all subjects and ignore treatment assignment.

For logarithmic transformations of seizure frequency, the natural logarithm will be used and a value of 1 will be added prior to performing the transformation.

For analyses and summaries of subjects while taking UX007, the time while taking placebo will be excluded and the original baseline will be used for all subjects regardless of which treatment was taken during the double-blind placebo-controlled treatment period.

Graphical displays of select study endpoints will be completed and include both observed study data and modeled analyses. Arithmetic means, least square means (LSM), and appropriate measure of dispersion (e.g., standard deviation, standard error) or confidence intervals may be displayed in figures.

8.2 Subject Accountability

The number and percentage of subjects in each of the analysis populations (Screened, Randomized, Efficacy, Per Protocol, Safety, Extension, PK) will be summarized by treatment group and overall.

Screen-failure subjects (i.e., subjects screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the Screened Population. The number and percentage of subjects in the Randomized Population who complete the

double-blind placebo-controlled treatment period, who complete the open-label extension period and who prematurely discontinue will be presented for each treatment group and overall. The reasons for early discontinuation will be summarized.

8.2.1 Protocol Deviations

Protocol deviations will be summarized for the Efficacy Analysis Set and listed by type.

8.3 Demographics

A table will be presented for the Efficacy Analysis Set by treatment group and overall for the following variables:

- Ethnicity
- Race
- Age at informed consent and age group using the following categories:
  - Under 2
  - 2 to less than 12
  - 12 to less than 18
  - 18 to less than 65
  - 65 and above

A table will be presented by treatment group and overall, by Age at informed consent (Pediatrics under 18 vs. Adults 18 and above), for the following variables:

- Ethnicity
- Race
- Sex

8.4 Disease Characteristics and Medical History

Summary statistics will be presented for the Efficacy Analysis Set by treatment group and overall, by age at informed consent (under 18 vs. 18 and above), for the following variables:

- Time at randomization since Glut1 DS diagnosis by mutation analysis
- Glut1 DS mutation description
- Glut1 DS symptoms history including whether ongoing: seizures, walking abnormality, coordination or motor abnormalities besides walking, paroxysmal exertional dyskinesia, movement disorder besides PED, cognitive abnormality, behavioral abnormality, developmental delay

- Ketogenic diet history (yes/no)
- Seizure history by type: Generalized Tonic-Clonic, Generalized Tonic, Generalized Clonic, Generalized Atonic, Partial/Focal with Secondary Generalization, Myoclonic, Myoclonic (Astatic) Atonic, Myoclonic Tonic, Complex Partial/Focal, Simple Partial/Focal Motor, Simple Partial/Focal Sensory, Simple Partial/Focal Psychological, Typical Absence, Atypical Absence, Absence with Special Features (Myoclonic absence), Absence with Special Features (Eyelid myoclonia), Unclassified (Inc. epileptic spasms)
- Average number of observable seizures (generalized [except absence] or partial-onset seizures) per month over the last 6 months

Listings will be provided for the following:

- Medical history: major illnesses, diagnoses, and surgeries

8.5 IP Administration

8.5.1 Study Drug Exposure

Duration of IP exposure and duration of UX007 exposure will be summarized by study period, and by treatment group, for subjects while taking UX007, and overall. A listing will also be provided.

8.5.2 Dose Titration

Summary statistics for dose titration will be presented by treatment group, and overall, for the Efficacy Analysis Set. The following parameters will be summarized:

- Missed Dose (Yes/No)
- Reason Dose Missed
- Total Daily Dose Taken (ml)
- Tolerability Issues (Yes/No)
- Target Dose (ml)

A listing will also be provided.

8.5.3 Diet Diary Review

The following measures will be summarized by visit based on the 3 day Diet Diary Review for the 3 days prior to each visit:

- Average Study Drug Calories, the average of the 3 entries for Study Drug

- Average Total Daily Calories
- Maximum Tolerated Dose Achieved (%)
- Maximum Tolerated Dose Achieved ≥20% (yes/no)
- Prescribed Dose through next visit (ml)

A listing will also be provided.

8.5.4 Dosing Compliance

Number and percent of days missed will be summarized for the titration period, the double-blind placebo-controlled treatment period and the open-label extension period.

8.6 Efficacy Analyses

The statistical approach for each efficacy analysis is summarized in Table 5 and will depend on the level of endpoint (primary, secondary, exploratory) and the study periods involved (double-blind placebo-controlled treatment, open-label extension). The statistical approach for Week 8 analyses of primary and secondary endpoints will be comparisons between UX007 and placebo. A more thorough table showing Test/Instrument, Eligible Study Population, Endpoint, Subjects Applicable, Endpoint Level, Timepoints for Assessments, and Statistical Approach by Study Period Analysis is provided in Appendix A. The statistical approach is defined for the following study period analyses:

- Week 8 Analyses: incorporate data up to the end of the double-blind placebo-controlled treatment period
- Week 52 Analyses: incorporate data from the entire study

Each statistical approach is described in the following sections.

Table 5: Efficacy Analyses by Study Period and Endpoint Level

Endpoint Level	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
Primary and Secondary Endpoints	Comparison Between UX007 and Placebo Groups	Estimation by Treatment Group and Overall
Exploratory Endpoints	Summary Statistics by Treatment Group	Summary Statistics by Treatment Group and Overall
Exploratory Endpoints at Select Sites	Data Listing	Data Listing

8.6.1 Comparisons Between UX007 and Placebo Groups

Comparisons of primary and secondary endpoints will be performed to test for a difference in the endpoint between UX007 and placebo groups during the double-blind placebo-controlled treatment period. Model based estimates will be presented, with 90% confidence intervals, for each endpoint by treatment group and also for the treatment effect (difference between treatment groups for continuous endpoints and difference between treatment groups for binary endpoints).

Endpoints measured during the double-blind placebo-controlled treatment period only at Week 8 and those measured at both Week 4 and Week 8 will be analyzed differently as described below. Endpoints measured only at Week 8 include those derived from the seizure diary and EEG. Endpoints measured at both Week 4 and Week 8 included those derived from CANTAB, 6MWT and GMFM-88.

Continuous Endpoints:

- Continuous endpoints measured only at Week 8 will be analyzed using linear regression (ANCOVA), with change from baseline to Week 8 as the response variable, treatment group (UX007 vs. placebo) as the primary variable of interest and an appropriate baseline value as an additional covariate.
- Continuous endpoints measured at both Week 4 and Week 8 will be analyzed using generalized estimating equations (GEE), with change from baseline at each timepoint as the response variable; treatment group (UX007 vs. placebo), a factor for visit, visit by treatment interaction and an appropriate baseline value as covariates; identity link function and exchangeable within subject working correlation matrix. The comparison of interest will be based on the LS means difference at Week 8.

Binary Endpoints:

- Categorical (binary) endpoints measured only at Week 8 will be analyzed using logistic regression, with a yes/no indicator as the response variable, treatment group (UX007 vs. placebo) as the primary variable of interest and an appropriate baseline value as an additional covariate.
- Categorical (binary) endpoints measured at both Week 4 and Week 8 will be analyzed using generalized estimating equations (GEE), with a yes/no indicator at each timepoint as the response variable; treatment group (UX007 vs. placebo), a factor for visit, visit by treatment interaction and an appropriate baseline value as covariates; logit link function and exchangeable within subject working correlation matrix. The comparison of interest will be based on the LS means difference at Week 8.

If the number of observations is insufficient for analyses, between group comparisons may not be done and within group tests for no change from baseline may be provided instead.

8.6.2 Estimation by Treatment Group and Overall

Estimation by randomized treatment group, for subjects while taking UX007 and overall will be done over time will be analyzed using a generalized estimation equations (GEE) model as follows:

- Continuous endpoints will be analyzed using a GEE linear model, with change from baseline at each timepoint as the response variable; treatment group (UX007 vs. placebo), a factor for visit, visit by treatment interaction and an appropriate baseline value as covariates; identity link function and exchangeable within subject working correlation matrix.
- Categorical (binary) endpoints will be analyzed using a GEE logistic model, with a yes/no indicator at each timepoint as the response variable; treatment group (UX007 vs. placebo), a factor for visit, visit by treatment interaction and an appropriate baseline value as covariates, logit link function and exchangeable within subject working correlation matrix.

All available measurements during the appropriate study period will be included in the model.

If the number of observations is insufficient for analyses, summary statistics will be provided.

8.6.3 Primary Efficacy Endpoint

The primary efficacy endpoint is the reduction from baseline to week 8 in frequency of seizures (normalized to a 4-week rate): observable seizures measured for 6 weeks after 2-week titration by diary and absence seizures measured overnight by electroencephalography (EEG). Observable seizure frequency at baseline will be calculated based on approximately 6 weeks between the screening and randomization visits and observable seizure frequency at week 8 will be calculated based on approximately 6 weeks between the end of titration and the week 8 visit (see Section 5.7.1). Absence seizure frequency will be based on overnight EEG at the randomization and week 8 visits.
The primary efficacy endpoint will be derived for each subject based on subject seizure type at randomization: observable seizures from the diary will be used for Observable Seizures Subjects and absence seizures from EEG will be used for Absence Seizures Only Subjects (see Section 5.6).

The primary efficacy endpoint will be analyzed, based on the Efficacy Analysis Set, using a linear regression (ANCOVA) model as described for continuous endpoints in Section 8.6.1. Logarithmic transformations will be used for modeling. The response variable in the model will be the reduction in the natural logarithm of the seizure frequency (+ 1) from baseline to Week 8 and the baseline covariate will be the natural logarithm of the baseline seizure frequency (+ 1): observable seizures from the diary will be used for Observable Seizures Subjects and absence seizures from EEG will be used for Absence Seizures Only Subjects.

An additional covariate will be included that indicates whether the subject is an Observable Seizures Subject or an Absence Seizures Only Subject. Estimates and 90% confidence intervals of percent reduction in seizure frequency will be derived from the model for each treatment group and for the difference between groups.

Missing data will be imputed as specified in Section 7.1. Sensitivity analysis assessing the impact of missing data will be performed using the methods described in Section 7.1.

Percent reduction from baseline in frequency of seizures over the entire study period will be summarized by visit (see Section 5.7.1), and by treatment group, for subjects while taking UX007, and overall.

The following additional analyses will be performed:

- An analysis will be performed incorporating multiplicity adjustment for analyses of absence and observable seizures using a fallback method (Wiens et al. 2005). The absence seizures and observable seizures analyses may include overlapping subjects. For each of these subgroups, a within UX007 group test will be performed first and the between group test will only be performed if the p-value for the within group test is less than the appropriate level according to the procedure. The one-sided type I error (α=0.05) will be split into 3 components: α_1(Overall) = 0.04, α_2(Absence) = 0.005, α_3(Observable) = 0.005. The following null hypotheses will be tested:
  - H_{01}(Overall, Between Group): Reduction from baseline to week 8 in frequency of seizures with UX007 is not greater than with placebo
  - H_{02W}(Absence, Within Group): Reduction from baseline to week 8 in frequency of *absence* seizures with UX007 is not greater than zero
  - H_{02B}(Absence, Between Group): Reduction from baseline to week 8 in frequency of *absence* seizures with UX007 is not greater than with placebo
  - H_{03W}(Observable, Within Group): Reduction from baseline to week 8 in frequency of *observable* seizures with UX007 is not greater than zero
  - H_{03B}(Observable, Between Group): Reduction from baseline to week 8 in frequency of *observable* seizures with UX007 is not greater than with placebo

  The corresponding nominal p-values are defined as p_1(Overall), p_{2W}(Absence), p_{2B}(Absence), p_{3W}(Observable), p_{3B}(Observable). The testing procedure will be performed as follows:

  1. If $p_1 \leq \alpha_1 = 0.04$, then reject H_{01} and set $\alpha_2^* = \alpha_1 + 0.005$; otherwise, accept H_{01} and set $\alpha_2^* = 0.005$.
  2. If $p_{2W} \leq \alpha_2^*$, then reject H_{02W}; otherwise, accept H_{02W}, accept H_{02B} and set $\alpha_3^* = 0.005$.
  3. If $p_{2W} \leq \alpha_2^*$ *and* $p_{2B} \leq \alpha_2^*$, then reject H_{02B} and set $\alpha_3^* = \alpha_2 + 0.005$; otherwise, accept H_{02B} and set $\alpha_3^* = 0.005$.

4. If $p_{3W} \leq \alpha_3^*$, then reject H_{03W}; otherwise, accept H_{03W} and accept H_{03B}.
5. If $p_{3W} \leq \alpha_3^*$ *and* $p_{3B} \leq \alpha_3^*$, then reject H_{03B}; otherwise, accept H_{02B}.

- An analysis will be performed with seizure frequency at baseline and Week 8 derived for each subject based on subject seizure type at randomization: observable seizures from the diary will be used for Observable Seizures Only Subjects and absence seizures from EEG will be used for Absence Seizures Subjects (see Section 5.6).
- An analysis will be performed using observable seizure frequency at week 8, including titration period, calculated based on seizure diary data collected for approximately 8 weeks from baseline to week 8.
- An analysis will be performed using the Per Protocol Analysis Set.
- An analysis will be performed using the alternative imputation methods described in Section 7.1.

8.6.4 Secondary Endpoints

For secondary endpoints, between group comparisons from baseline to week 8 will be performed as described in Section 8.6.1 as follows:

- Seizure response at Week 8 (a percent reduction from baseline in seizure frequency greater than or equal to 50%, see Section 5.7.4) will be analyzed, based on the Efficacy Analysis Set, using logistic regression. The baseline covariate will be the natural logarithm of the baseline seizure frequency (+ 1): observable seizures from the diary will be used for Observable Seizures Subjects and absence seizures from EEG will be used for Absence Seizures Only Subjects. An additional covariate will be included that indicates whether the subject is an Observable Seizures Subject or an Absence Seizures Only Subject.
- Reduction from baseline in frequency of observable seizures will be analyzed, based on the Efficacy Analysis Set, using linear regression. The response variable in the model will be the change in the natural logarithm of the observable seizure frequency (+ 1) from baseline to Week 8 and the baseline covariate will be the natural logarithm of the baseline frequency (+ 1) of observable seizures (see Section 5.7.5). Estimates and 90% confidence intervals of percent reduction in observable seizure frequency will be derived from the model for each treatment group and for the difference between groups.
- Observable seizure response at Week 8 will be analyzed, based on the Efficacy Analysis Set, using logistic regression. Observable seizure frequency will be calculated based on approximately 6 weeks between the end of titration and the week 8 visit. The baseline covariate will be the natural logarithm of the baseline frequency (+ 1) of observable seizures (see Section 5.7.5).
- Reduction from baseline in frequency of absence seizures will be analyzed, based on the Efficacy Analysis Set, using linear regression. The response variable in the model will be

the change in the natural logarithm of the absence seizure frequency (+ 1) from baseline to Week 8 and the baseline covariate will be the natural logarithm of the baseline frequency (+ 1) of absence seizures. Estimates and 90% confidence intervals of percent reduction in absence seizure frequency will be derived from the model for each treatment group and for the difference between groups.

- Absence seizure response at Week 8 will be analyzed, based on the Efficacy Analysis Set, using logistic regression. The baseline covariate will be the natural logarithm of the baseline frequency (+ 1) of absence seizures.
- Change from baseline in each of the 8 CANTAB scores will be analyzed, based on the Efficacy Analysis Set – CANTAB, using GEE with identity link function. The baseline covariate will be the baseline value of the corresponding CANTAB score.
- Change from baseline in 6MWT distance traveled (in meters and percent predicted) will be analyzed, based on the Efficacy Analysis Set – 6MWT, using GEE with identity link function. The baseline covariate will be the baseline value of the corresponding 6MWT measure.
- Since a high proportion of subjects do not experience onset of PED during the 6MWT, onset of PED will be analyzed as a binary indicator for whether PED occurred (yes/no). Onset of paroxysmal exertional dyskinesia (PED) during the 6MWT (yes/no) will be analyzed, based on the Efficacy Analysis Set – 6MWT, using GEE with logistic link function. The baseline covariate will be the baseline value of the indicator for onset of PED.
- Change from baseline in GMFM-88 Total score will be analyzed, based on the Efficacy Analysis Set – GMFM-88, using GEE with identity link function. The baseline covariate will be the baseline value of GMFM-88 Total score.

Missing data will be imputed as specified in Section 7.1.

Each endpoint will be summarized by visit, by treatment group, for subjects while taking UX007, and overall.

The following additional analyses will be performed:

- An analysis will be performed using the Per Protocol Analysis Set for endpoints involving all seizures, and the Per Protocol Analysis Set – Observable Seizures for endpoints involving seizures from the diary only, the Per Protocol Analysis Set – Absence Seizures for endpoints involving seizures from EEG only, and the Per Protocol Analysis Set – CANTAB for the CANTAB endpoints (see Section 6.4).
- For seizure response, an analysis will be performed with seizure frequency at baseline and Week 8 derived for each subject based on subject seizure type at randomization: observable seizures from the diary will be used for Observable Seizures Only Subjects and absence seizures from EEG will be used for Absence Seizures Subjects (see Section 5.6).

- For endpoints involving seizures, an analysis will be performed using the alternative imputation methods described in Section 7.1.
- For endpoints involving observable seizures from the seizure diary, an analysis will be performed using observable seizure frequency at week 8, including titration period, calculated based on seizure diary data collected for approximately 8 weeks from baseline to week 8.

8.6.5 Exploratory Efficacy Endpoints

Summary statistics, including p-values for differences between treatment groups during the double-blind placebo-controlled treatment period, will be provided by visit for the following exploratory endpoints over the entire study period by treatment group and overall: specific seizure types derived from seizure diary, specific seizure types derived from EEG, CNS, CGI-I, SF-10 and SF-12 v2.

A data listing will be provided for the following exploratory endpoints available at select sites over the entire study period: PPVT, PEDI-CAT, Gait analysis during 6-minute walk test (6MWT), GMFM-88 domains (lying/rolling, sitting, crawling/kneeling, standing, and walking/running/jumping), Beery-VMI and RCPM.

8.6.6 Subset Analyses of Primary and Select Secondary Endpoints

Analyses of primary and secondary endpoints involving seizures will be repeated for the following subgroups: Efficacy Analysis Set – Observable Seizures and Efficacy Analysis Set – Absence Seizures, for the subjects with ≥80% dosing compliance from baseline to week 8 (see Section 8.5.4).

8.7 Safety Analyses

All safety analyses will be based on the Safety Analysis Set. In general safety analyses will be completed using summary statistics, graphs or subject listings. No planned inferential testing of safety endpoints is planned. If after the planned analysis it is determined by the medical writer and study medical monitor that inferential tests of significance may help to provide context for safety information these tests may be performed and identified in the CSR. Summaries will be done by study period and overall.

Analyses and summaries will be performed by study period, by treatment group, for subjects while taking UX007, and overall.

8.7.1 Adverse Events

Adverse Events will be assessed at all visits and throughout the course of the study. An AE will be considered a treatment emergent adverse event (TEAE) if it occurs or worsens in severity on or after the date of the first dose of study drug. An AE will be considered a UX007 emergent adverse event if it occurs or worsens in severity on or after the first date of

first dose of UX007 during the study. It is expected that the date of first dose of UX007 during the study will be the date of Randomization visit for the UX007 group and the date of Week 8 visit for the placebo group; however, the date of first UX007 dose actually received will be used.

UX007 emergent AEs will be summarized by SOC and preferred term during the period exposed to UX007 by treatment group and overall for all subjects who receive UX007. TEAEs will be summarized by SOC and preferred term during the course of the study by treatment group and overall for all subjects who receive study drug.

Exposure adjusted event incidence, defined as total number of occurrences of an event summed across all subjects in the group divided by the total observed time for events for subjects in the group, will be summarized for TEAEs and UX007 emergent AEs by SOC and preferred term by treatment group and overall.

During the double-blind placebo-controlled period; TEAEs will be summarized by treatment group and overall, and UX007 emergent AEs will be summarized by treatment group and overall. If no placebo subjects also receive UX007 during the double-blind placebo-controlled period, then there will only be one group for UX007 emergent AEs during the double-blind placebo-controlled period. During the open-label extension period, TEAEs and UX007 emergent AEs will both be summarized by treatment group and overall.

A high-level safety summary will display the numbers of subjects who experience one or more AEs in each of the following categories:

- All TEAEs and UX007 emergent AEs
- All treatment related TEAEs and UX007 emergent AEs
- Serious TEAEs and UX007 emergent AEs
- All treatment related SAEs and UX007 emergent SAEs
- Grade 3/4 TEAEs and UX007 emergent AEs
- TEAEs and UX007 emergent AEs leading to study discontinuation
- Fatal TEAEs and UX007 emergent AEs
- TEAEs and UX007 emergent AEs in the GI SMQ (see Appendix C)
- Related TEAEs and UX007 emergent AEs in the GI SMQ

Reported AE terms were coded to MedDRA (version 17.1) lowest level terms (LLT) linked to preferred terms (PT) and system organ classes (SOC). The number and percent of subjects with any treatment-emergent adverse events (TEAEs) will be displayed by SOC and PT. Within each level of summarization (SOC or PT), subjects will be counted only once if they had more than one event at that level. The same summary will be performed for TEAEs in

the MedDRA GI SMQ, all related TEAEs, serious TEAEs, those causing discontinuation of investigational product and fatal TEAEs.

The number and percent of subject TEAEs will also be summarized by greatest reported severity grade (AE grading defined in study protocol) for each event preferred term.

The number and percent of subjects experiencing one or more TEAEs for each PT in the GI SMQ will be summarized.

The number and percent of subjects experiencing one or more TEAE, TESAEs, and treatment related TEAEs by descending PT will be summarized.

The number and percent of subjects experiencing one or more TEAE by SOC and PT in order of descending frequency will be summarized by age group (18 and older vs. under 18), gender and seizure type (Observable Seizures Subjects, Absence Seizures Only Subjects).

The number and percent of subjects who withdraw from the study or discontinue study medication due to a TEAE or SAE will be summarized.

The number and percent of subject TEAEs will be summarized by greatest reported relationship (relationship defined in protocol) to study medication.

All TEAEs will be listed individually by subject. In addition, a separate listing will be produced for AEs that are not treatment-emergent. Separate individual subject listings for SAEs and TEAEs leading to Study Withdrawal or discontinuation of Study Medication will also be produced.

8.7.2 Vital Signs and Weight

The following vital signs and weight will be summarized by time point for the observed value and the change from baseline value.

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

8.7.3 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.

8.7.4 Electrocardiogram

The following ECG results and change from baseline results will be summarized and provided in subject listing:

- RR Duration (msec)
- Heart Rate (beats/min)
- PR Duration (msec)
- QRS Duration (msec)
- QT Duration (msec)
- QTCB - Bazett's Correction Formula (msec)
- QTCF - Fridericia's Correction Formula (msec)
- Overall Statement (Categorical indicator of evaluability, abnormality and clinical significance of abnormality)

8.7.5 Select Clinical Laboratory Parameters

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

The following laboratory results will be summarized by time point for the observed value as well as for the change from baseline value:

- 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
- Hematology: Hematocrit, Hemoglobin, Platelet count, Red blood cell (RBC) count, White blood cell (WBC) count, Beta-hydroxybutyrate (BHB) (at Screening)
- Urinalysis: Appearance, Color, pH, Specific gravity, Ketones, Protein, Glucose, Pregnancy test (if applicable)

For fasting serum glucose, triglycerides, ALT, AST and GGT, CTCAE severity grades will be summarized in shift tables pairing each subject's baseline severity grade with the subject's highest post-baseline severity grade.

Specifically, CTCAE severity grades for increased triglycerides are:

- Grade 1: 150 – 300 mg/dL; 1.71 – 3.42 mmol/L
- Grade 2: > 300 – 500 mg/dL; > 3.42 – 5.7 mmol/L
- Grade 3: >500 – 1000 mg/dL; > 5.7 – 11.4 mmol/L
- Grade 4: >1000 mg/dL; > 11.4 mmol/L

CTCAE severity grades for hypoglycemia are:

- Grade 1: <LLN – 55 mg/dL; <LLN – 3.0 mmol/L
- Grade 2: <55 – 40 mg/dL; <3.0 – 2.2 mmol/L
- Grade 3: <40 – 30 mg/dL; <2.2 – 1.7 mmol/L
- Grade 4: < 30 mg/dL; <1.7 mmol/L

CTCAE severity grades for increased ALT and increased AST are:

- Grade 1: >ULN to 3.0 x ULN
- Grade 2: >3.0 x ULN to 5.0 x ULN
- Grade 3: >5.0 x ULN to 20.0 x ULN
- Grade 4: >20.0 x ULN

And CTCAE severity grades for increased GGT are:

- Grade 1: >ULN to 2.5 x ULN
- Grade 2: >2.5 x ULN to 5.0 x ULN
- Grade 3: >5.0 x ULN to 20.0 x ULN
- Grade 4: >20.0 x ULN

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.

8.7.6 Suicidal Ideation and Behavior

Assessment of suicidal ideation and behavior is a regular part of development programs involving AEDs and other neurologic drugs with central nervous system activity (FDA Draft Guidance 2012). The Columbia Suicide Severity Rating Scale (C-SSRS) is a standardized suicidal rating instrument used to assess the suicidal ideation and behavior in an at-risk pediatric population (Posner et al. 2011).

The following outcomes are C-SSRS categories and have binary responses (yes/no).
The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results.

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

- Suicidal ideation: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS
- Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS

C-SSRS endpoints will be summarized by treatment group and presented in a listing.

8.7.7 Prior and Concomitant Medications

A *prior medication* is defined as any medication started before the date of the first dose of study drug. A *concomitant medication* is defined as any medication taken on or after the date of the first dose of study drug. A medication started before the date of the first dose of study drug and also taken after the date of first dose of study drug 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 WHO Drug Dictionary Enhanced Version 2014 December or newer and summarized by treatment group for the Safety Analysis Set and listed by subject. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject would be counted only once for the coded drug name or therapeutic class.

8.7.8 Pharmacokinetics of UX007

Summary statistics, including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be presented over time for plasma peak levels of UX007, plasma levels of UX007 metabolites [C4 ketone (BHB), C5 ketones (beta-hydroxypentanoate [BHP]), and heptanoate], non-fasting BHB and trough (pre-dose [within 15 minutes]) UX007 at each available time point. Data will be listed for all subjects with available data. All subjects and samples excluded from the analysis will be clearly documented in the study report.

9 PLANNED DATA PRESENTATIONS

Data presentations planned to support writing the UX007G-CL201 CSR are listed in Table 6.

Table 6: Planned Data Presentations

Output Type	Title
	Demographic Data
Table	Subject Disposition – Randomized Population
Table	Protocol Deviations – Efficacy Analysis Set
Table	Demographics – Efficacy Analysis Set
Table	Demographics by Age Group – Efficacy Analysis Set
Table	Glut1 DS Disease History – Efficacy Analysis Set
Table	Seizure History – Efficacy Analysis Set
Table	Study Drug Exposure – Efficacy Analysis Set
Table	Summary of Diet Diary Review – Efficacy Analysis Set
Table	Dosing Compliance – Days Dose Missed by Study Period – Efficacy Analysis Set
	Primary and Secondary Efficacy Analyses – Seizures
Table	Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set
Table	Observable Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set
Table	Absence Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set
Table	Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set
Table	Observable Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set
Table	Absence Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set
Table	Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set
Table	Observable Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set
Table	Absence Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set
	Additional Efficacy Analyses – Seizures
Table	Seizures – Week 8 Analysis – Summary – Per Protocol Analysis Set
Table	Observable Seizures – Week 8 Analysis – Summary – Per Protocol Analysis Set
Table	Absence Seizures – Week 8 Analysis – Summary – Per Protocol Analysis Set
Table	Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Per Protocol Analysis Set
Table	Observable Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Per Protocol Analysis Set
Table	Absence Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Per Protocol Analysis Set
Table	Seizure Response – Week 8 Analysis – Logistic Regression – Per Protocol Analysis Set
Table	Observable Seizure Response – Week 8 Analysis – Logistic Regression – Per Protocol Analysis Set
Table	Absence Seizure Response – Week 8 Analysis – Logistic Regression – Per Protocol Analysis Set

Output Type	Title
Table	Absence Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set – Absence at Baseline
Table	Absence Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Absence at Baseline
Table	Absence Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Absence at Baseline
Table	Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Observable Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Absence Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Observable Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Absence Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Observable Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Absence Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Dosing Compliance ≥80%
Table	Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Alternate Imputation Method
Table	Observable Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Alternate Imputation Method
Table	Absence Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Alternate Imputation Method
Table	Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Alternate Imputation Method
Table	Observable Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Alternate Imputation Method
Table	Absence Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Alternate Imputation Method
Table	Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Complete Case Method
Table	Observable Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Complete Case Method
Table	Absence Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Complete Case Method
Table	Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Complete Case Method
Table	Observable Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Complete Case Method

Output Type	Title
Table	Absence Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Complete Case Method
Table	Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set –Alternate Seizure Frequency Derivation
Table	Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Alternate Seizure Frequency Derivation
Table	Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set –Alternate Seizure Frequency Derivation
Table	Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set –Analysis Including Dose Titration Period
Table	Observable Seizures – Week 8 Analysis – Summary – Efficacy Analysis Set –Analysis Including Dose Titration Period
Table	Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set – Analysis Including Dose Titration Period
Table	Observable Seizures – Reduction from Baseline – Week 8 Analysis – ANCOVA – Efficacy Analysis Set –Analysis Including Dose Titration Period
Table	Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set –Analysis Including Dose Titration Period
Table	Observable Seizure Response – Week 8 Analysis – Logistic Regression – Efficacy Analysis Set – Analysis Including Dose Titration Period
	Secondary Efficacy Analyses
Table	CANTAB Simple Choice Median Reaction Time – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB Five Choice Median Reaction Time – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB Simple Choice Standard Deviation – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB Spatial Span Length – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB Paired Associates Learning Test Total Errors (Adjusted) – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB Paired Associates Learning Test First Trial Memory Score – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB Spatial Working Memory Between Errors – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB Spatial Working Memory Strategy – Week 8 Analysis – Summary – Efficacy Analysis Set – CANTAB
Table	CANTAB – Change from Baseline – Week 8 Analysis – GEE – Efficacy Analysis Set – CANTAB
Table	CANTAB – Change from Baseline – Week 8 Analysis – GEE – Per Protocol Analysis Set – CANTAB
Table	6MWT Distance (meters) – Week 8 Analysis – Summary – Efficacy Analysis Set – 6MWT
Table	6MWT Distance (percent predicted) – Week 8 Analysis – Summary – Efficacy Analysis Set – 6MWT
Table	Onset of PED – Week 8 Analysis – Summary – Efficacy Analysis Set – 6MWT

Output Type	Title
Table	6MWT – Change from Baseline – Week 8 Analysis – GEE – Efficacy Analysis Set – 6MWT
Table	Onset ofPED – Week 8 Analysis – GEE – Efficacy Analysis Set – 6MWT
Table	GMFM-88 Total Score – Week 8 Analysis – Summary – Efficacy Analysis Set – GMFM-88
Table	GMFM-88 Total Score – Change from Baseline – Week 8 Analysis – GEE – Efficacy Analysis Set – GMFM-88
	Exploratory Efficacy Analyses
Table	Frequency of Seizure Types via Diary – Week 8 Analysis – Summary – Efficacy Analysis Set
Table	Frequency of Seizure Types via EEG – Week 8 Analysis – Summary – Efficacy Analysis Set
Table	CGI-S and CGI-I – Week 8 Analysis – Summary – Efficacy Analysis Set – CGI-I
Table	CGI-I – Week 8 Analysis – t-tests – Efficacy Analysis Set
Table	SF-10 – Week 8 Analysis – Summary – Efficacy Analysis Set – SF-10
Table	SF-12 v2 – Week 8 Analysis – Summary – Efficacy Analysis Set – SF-12
Table	SF-10 – Change from Baseline– Week 8 Analysis – t-tests – Efficacy Analysis Set
Table	SF-12 – Change from Baseline– Week 8 Analysis – t-tests – Efficacy Analysis Set
Table	CNS – Week 8 Analysis – Summary – Efficacy Analysis Set – CNS
Table	CNS – Change from Baseline – Week 8 Analysis – t-tests – Efficacy Analysis Set
	Safety Analyses of Adverse Events
Table	Overall Summary of Adverse Events – Safety Analysis Set
Table	Overall Summary of Adverse Events by Study Period – Safety Analysis Set
Table	Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Severity – Safety Analysis Set
Table	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Greatest Reported Relationship – Safety Analysis Set
Table	Grade 3 or 4 Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table	Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table	Gastrointestinal Treatment Emergent Adverse Events by Preferred Term – Safety Analysis Set
Table	UX007 Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table	Serious UX007 Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table	Related Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table	Related Gastrointestinal Treatment Emergent Adverse Events by Preferred Term – Safety Analysis Set
Table	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (by age group) – Safety Analysis Set

Output Type	Title
Table	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (by gender) – Safety Analysis Set
Table	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (by seizure type) – Safety Analysis Set
Table	Treatment Emergent Adverse Events by Preferred Term – Safety Analysis Set
Table	Serious Treatment Emergent Adverse Events by Preferred Term – Safety Analysis Set
Table	Related Treatment Emergent Adverse Events by Preferred Term – Safety Analysis Set
Table	Exposure Adjusted Treatment Emergent Adverse Event Incidence by System Organ Class and Preferred Term – Safety Analysis Set
Table	Exposure Adjusted UX007 Emergent Adverse Event Incidence by System Organ Class and Preferred Term – Safety Analysis Set
	Safety Analyses of Laboratory and Other Parameters
Table	Chemistry Laboratory Data Summary – Safety Analysis Set
Table	Chemistry Laboratory Shift Table – Safety Analysis Set
Table	Hematology Laboratory Data Summary – Safety Analysis Set
Table	Hematology Laboratory Shift Table – Safety Analysis Set
Table	Urinalysis Laboratory Data Summary – Safety Analysis Set
Table	Urinalysis Laboratory Shift Table – Safety Analysis Set
Table	Chemistry Abnormal and/or Clinically Significant Findings – Safety Analysis Set
Table	Hematology Abnormal and/or Clinically Significant Findings – Safety Analysis Set
Table	Urinalysis Abnormal and/or Clinically Significant Findings – Safety Analysis Set
Table	Vital Signs and Weight Summary – Safety Analysis Set
Table	ECG Results Summary – Safety Analysis Set
Table	ECG Results Shift Table – Safety Analysis Set
Table	Hy's Law Status Shift Table – Safety Analysis Set
Table	PK Parameters Summary – Safety Analysis Set
Table	Suicidal Ideation Summary – Safety Analysis Set
	Efficacy Analyses Figures
Figure	Seizures – Week 8 Analysis – Individual and Geometric Mean with 90% CI – Efficacy Analysis Set
Figure	Observable Seizures – Week 8 Analysis – Individual and Geometric Mean with 90% CI – Efficacy Analysis Set – Observable Seizures
Figure	Observable Seizures – Week 8 Analysis – Individual and Geometric Mean with 90% CI – Efficacy Analysis Set – Observable Seizures Only
Figure	Absence Seizures – Week 8 Analysis – Individual and Geometric Mean with 90% CI – Efficacy Analysis Set – Absence Seizures
Figure	Absence Seizures – Week 8 Analysis – Individual and Geometric Mean with 90% CI – Efficacy Analysis Set – Absence Seizures Only
Figure	Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 – Cumulative Distribution Function – Efficacy Analysis Set
Figure	Observable Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 – Cumulative Distribution Function – Efficacy Analysis Set – Observable Seizures

Output Type	Title
Figure	Observable Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 – Cumulative Distribution Function – Efficacy Analysis Set – Observable Seizures Only
Figure	Absence Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 – Cumulative Distribution Function – Efficacy Analysis Set – Absence Seizures
Figure	Absence Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 – Cumulative Distribution Function – Efficacy Analysis Set – Absence Seizures Only
Figure	Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 with 90% CI – Efficacy Analysis Set
Figure	Seizure Response – Week 8 Analysis – Efficacy Analysis Set
Figure	Observable Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 with 90% CI – Efficacy Analysis Set
Figure	Observable Seizure Response – Week 8 Analysis – Efficacy Analysis Set
Figure	Absence Seizures – Week 8 Analysis – Percent Reduction from Baseline to Week 8 with 90% CI – Efficacy Analysis Set
Figure	Absence Seizure Response – Week 8 Analysis – Efficacy Analysis Set
Figure	CANTAB Simple Choice Median Reaction Time – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	CANTAB Five Choice Median Reaction Time – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	CANTAB Simple Choice Standard Deviation – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	CANTAB Spatial Span Length – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	CANTAB Paired Associates Learning Test Total Errors (Adjusted) – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	CANTAB Paired Associates Learning Test First Trial Memory Score – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	CANTAB Spatial Working Memory Between Errors – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	CANTAB Spatial Working Memory Strategy – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	6MWT Distance (meters) – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	6MWT Distance (percent predicted) – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	GMFM-88 Total Score – Week 8 Analysis – Individual and Mean with 90% CI – Efficacy Analysis Set
Figure	SF-10 – Week 8 Analysis – Efficacy Analysis Set
Figure	SF-12 – Week 8 Analysis – Efficacy Analysis Set
Figure	CGI-I – Week 8 Analysis – Efficacy Analysis Set
	Demographics Listings
Listing	Subject Disposition – Randomized Population
Listing	Analysis Sets – Randomized Population

Output Type	Title
Listing	Subjects Who Failed to Meet One or More Inclusion/Exclusion Criteria – Screened Population
Listing	Protocol Deviations – Screened Population
Listing	Demographics and Baseline Characteristics – Randomized Population
Listing	Glut1 DS Disease Diagnosis and History – Screened Population
Listing	Ketogenic Diet History – Screened Population
Listing	Seizure History – Screened Population
Listing	Medical History – Screened Population
Listing	Prior and Concomitant Medications – Screened Population
Listing	Study Drug Dosing – Randomized Population
Listing	Dosing Compliance and Missed Doses – Randomized Population
	Efficacy Listings
Listing	Seizures – Randomized Population
Listing	Seizure Classification by Diary – Seizure Frequency by Type – Randomized Population
Listing	Seizure Classification by EEG – Seizure Frequency by Type – Randomized Population
Listing	CANTAB – Randomized Population
Listing	6MWT – Randomized Population
Listing	GMFM-88 Scores – Randomized Population
Listing	CGI-I – Randomized Population
Listing	SF-10 – Randomized Population
Listing	SF-12 v2 Questions – Randomized Population
Listing	SF-12 v2 Domain and Component Scores – Randomized Population
Listing	CNS – Randomized Population
Listing	PPVT – Randomized Population
Listing	PEDI-CAT – Randomized Population
Listing	Beery-VMI and Raven's Coloured Progressive Matrices – Randomized Population
Listing	Gait Analysis – Randomized Population
	Safety Listings
Listing	Treatment Emergent Adverse Events – Safety Analysis Set
Listing	Serious Treatment Emergent Adverse Events – Safety Analysis Set
Listing	UX007 Emergent Adverse Events – Safety Analysis Set
Listing	Serious UX007 Emergent Adverse Events – Safety Analysis Set
Listing	Adverse Events During the Run-In Period – Safety Analysis Set
Listing	Adverse Events Leading to Withdrawal from Study or Discontinuation from Study Drug – Safety Analysis Set
Listing	Treatment Emergent Adverse Events Leading to Death – Safety Analysis Set
Listing	Chemistry Laboratory Data – Safety Analysis Set
Listing	Hematology Laboratory Data – Safety Analysis Set
Listing	Urinalysis Laboratory Data – Safety Analysis Set

Output Type	Title
Listing	PK Data – Safety Analysis Set
Listing	Suicidal Ideation – Safety Analysis Set
Listing	Vital Signs and Weight – Safety Analysis Set
Listing	ECG – Safety Analysis Set
Listing	Laboratory Results and Hy's Law – Safety Analysis Set

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11 APPENDICES

Appendix A: Efficacy Endpoint Summary Table

Appendix B: Schedule of Events

Appendix C: Gastrointestinal Standardized MedDRA Query

Appendix D: SAS Code for Primary Statistical Analysis

APPENDIX A EFFICACY ENDPOINT SUMMARY TABLE

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
Seizure Diary + EEG	Efficacy Analysis Set	Reduction from baseline in frequency of seizures	All	Primary	Diary: daily from Screening to 52/ET; EEG: Screening, Randomization, Week 8, 26, 31	ANCOVA	Estimation
Seizure Diary + EEG	Efficacy Analysis Set	Seizure response	All	Secondary	Diary: daily from Screening to 52/ET; EEG: Screening, Randomization, Week 8, 26, 31	Logistic Regression	Estimation
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of observable seizures	All	Secondary	Daily from Screening to 52/ET	ANCOVA	Estimation
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Observable seizure response	All	Secondary	Daily from Screening to 52/ET	Logistic Regression	Estimation
EEG	Efficacy Analysis Set – Absence Seizures	Reduction from baseline in frequency of absence seizures	All	Secondary	Screening, Randomization, Week 8, 26, 31	ANCOVA	Estimation
EEG	Efficacy Analysis Set – Absence Seizures	Absence seizure response	All	Secondary	Screening, Randomization, Week 8, 26, 31	Logistic Regression	Estimation
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB RTI Simple Choice Median Reaction Time (RTIMDSRT)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB RTI Five Choice Median Reaction Time (RTIMDFRT)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB RTI Simple Choice Standard Deviation (RTISRTSD)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB SSP Span Length (SSPSLF)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB PAL Total Errors (Adjusted) (PALTEA)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB PAL First Trial Memory Score (PALFTMS)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB SWM Between Errors (SWMBE48)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
CANTAB	Efficacy Analysis Set	Change from baseline in CANTAB SWM Strategy (SWMS68)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
6-minute walk test (6MWT)	Efficacy Analysis Set	Change from baseline in 6MWT distance traveled (in meters)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
6-minute walk test (6MWT)	Efficacy Analysis Set	Change from baseline in 6MWT distance traveled (in percent predicted)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
6-minute walk test (6MWT)	Efficacy Analysis Set	Time (in minutes) to onset of paroxysmal exertional dyskinesia (PED)	All	Secondary	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Logistic	Estimation
GMFM-88	Efficacy Analysis Set	Change from baseline in GMFM-88 Total score	Select Sites	Secondary	Randomization, Week 4, 8, 26, 31, 36, 52, ET	GEE Linear	Estimation
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of generalized tonic-clonic seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of generalized tonic seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of generalized clonic seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of generalized atonic seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of partial/focal with secondary generalization seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of myoclonic seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of myoclonic atonic seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of myoclonic tonic seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of complex partial/focal seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of simple partial/focal motor seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of simple partial/focal sensory seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of simple partial/focal psychological seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of typical absence seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of atypical absence seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of myoclonic absence seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of absence eyelid myoclonia seizures	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
Seizure Diary	Efficacy Analysis Set – Observable Seizures	Reduction from baseline in frequency of unclassified seizures including epileptic spasms	All	Exploratory	Daily from Screening to 52/ET	Summary Statistics	Summary Statistics
CNS	Efficacy Analysis Set	Change from baseline in CNS Total Score	All	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
CGI-I	Efficacy Analysis Set	CGI Improvement scale	All	Exploratory	Randomization, Week 8, 26, 31, 36, 52, ET	Summary Statistics	Summary Statistics
SF-10	Efficacy Analysis Set	Change from baseline in SF-10 Physical Summary Score (PHS-10)	Ages 5-17	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-10	Efficacy Analysis Set	Change from baseline in SF-10 Psychosocial Summary Score (PSS-10)	Ages 5-17	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Physical Functioning (PF) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Role Limitations due to Physical Health (RP) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Bodily Pain (BP) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in General Health Perceptions (GH) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
SF-12 v2	Efficacy Analysis Set	Change from baseline in Vitality (VT) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Social Functioning (SF) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Role Limitations due to Emotions Problems (RE) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Mental Health (MH) score	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Physical Component Summary Scale (PCS-12)	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
SF-12 v2	Efficacy Analysis Set	Change from baseline in Mental Component Summary Scale (MCS-12)	Ages 18+	Exploratory	Randomization, Week 8, 26, 52, ET	Summary Statistics	Summary Statistics
PPVT	Efficacy Analysis Set	Change from baseline in PPVT standardized score	Select Sites	Exploratory	Screening, Week 8, 26, 31, 36, 52, ET	Summary Statistics	Summary Statistics

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
PEDI-CAT	Efficacy Analysis Set	Change from baseline in Daily Activities score	Select Sites	Exploratory	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
PEDI-CAT	Efficacy Analysis Set	Change from baseline in Mobility score	Select Sites	Exploratory	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
PEDI-CAT	Efficacy Analysis Set	Change from baseline in Social/Cognitive score	Select Sites	Exploratory	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
PEDI-CAT	Efficacy Analysis Set	Change from baseline in Responsibility score	Select Sites	Exploratory	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
Gait analysis during 6-minute walk test (6MWT)	Efficacy Analysis Set	Change from baseline in stride length	Select Sites	Exploratory	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
Gait analysis during 6-minute walk test (6MWT)	Efficacy Analysis Set	Change from baseline in velocity	Select Sites	Exploratory	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
Gait analysis during 6-minute walk test (6MWT)	Efficacy Analysis Set	Change from baseline in cadence	Select Sites	Exploratory	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
Gait analysis during 6-minute walk test (6MWT)	Efficacy Analysis Set	Change from baseline in base of support	Select Sites	Exploratory	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
Gait analysis during 6-minute walk test (6MWT)	Efficacy Analysis Set	Change from baseline in percentage of cycle time spent in double support	Select Sites	Exploratory	Screening, Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
GMFM-88	Efficacy Analysis Set	Change from baseline in GMFM-88 Lying and Rolling score	Select Sites	Secondary	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
GMFM-88	Efficacy Analysis Set	Change from baseline in GMFM-88 Sitting score	Select Sites	Secondary	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
GMFM-88	Efficacy Analysis Set	Change from baseline in GMFM-88 Crawling and Kneeling score	Select Sites	Secondary	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
GMFM-88	Efficacy Analysis Set	Change from baseline in GMFM-88 Standing score	Select Sites	Secondary	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing
GMFM-88	Efficacy Analysis Set	Change from baseline in GMFM-88 Walking, Running and Jumping score	Select Sites	Secondary	Randomization, Week 4, 8, 26, 31, 36, 52, ET	Data Listing	Data Listing

Test / Instrument	Eligible Study Population	Endpoint	Subjects Applicable	Endpoint Level	Timepoints for Assessments	Statistical Approach: Week 8 Analyses	Statistical Approach: Week 52 Analyses
Beery-VMI	Efficacy Analysis Set	Change from baseline in standard score	Select Sites	Exploratory	Screening, Week 8, 26, 52, ET	Data Listing	Data Listing
RCPM	Efficacy Analysis Set	Change from baseline in total score	Select Sites	Exploratory	Screening, Week 8, 26, 52, ET	Data Listing	Data Listing

APPENDIX B SCHEDULE OF EVENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX C GASTROINTESTINAL STANDARDIZED MEDDRA QUERY

Table 7 shows the MedDRA PTs that 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.

Table 7: Gastrointestinal SMQs

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	

APPENDIX D SAS CODE FOR PRIMARY STATISTICAL ANALYSIS