Statistical Analysis Plan

NCT Number: NCT03635073

Title: A Phase 2, Prospective, Interventional, Open-Label, Multi-Site, Extension Study to Assess the Long-Term Safety and Tolerability of Soticlestat (TAK-935) as Adjunctive Therapy in Subjects With Developmental Epileptic Encephalopathies Including Dravet Syndrome, Lennox Gastaut Syndrome, CDKL5 Deficiency Disorder, and Chromosome 15 Duplication Syndrome (ENDYMION 1)

Study Number: TAK-935-18-001

Document Version and Date: Version 4.0, 15 Apr 2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-935-18-001

Study Title:

A Phase 2, Prospective, Interventional, Open-Label, Multisite, Extension Study To Assess the Long-Term Safety and Tolerability of Soticlestat (TAK-935) as Adjunctive Therapy in Subjects With Developmental Epileptic Encephalopathies Including Dravet Syndrome, Lennox Gastaut Syndrome, CDKL5 Deficiency Disorder, and Chromosome 15 Duplication Syndrome
(ENDYMION 1)

Phase: 2

Version: Version 4.0

Date: 15-April-2024

Prepared by: [redacted], Ph.D.

Based on:

Protocol Version: Amendment 4

Protocol Date: 24 August 2021

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version (Version 2.0 prepared by Ovid Therapeutics Inc.)	06-AUG-2020	Not applicable.
Version 3 (prepared by Takeda)	01-March-2022	To implement Takeda SAP template and make consistent with Protocol Amendment 4; Clarifications added to the analysis of endpoints such as C-SSR, ophthalmological evaluations etc.
Version 4 (prepared by Takeda)	10-April-2024	To add analysis for potentially clinically significant clinical laboratory test values, vital signs, weight, height, and ECG evaluations. To update Ophthalmological Evaluations by adding visual confrontations and clarity how visual acuity will be summarized. To add additional exploratory analyses to explore growth trends in height and weight for 18 years old or younger subjects. Clarify analyses of [redacted] efficacy response. Added baseline consideration for analyzing [redacted] Visual Acuity. Added clarification on selecting records from multiple records from an analysis visit window. Additional clarification and technical details added, if deemed necessary. Updated the definition of categories based on Columbia-Suicide Severity Rating Scale (C-SSRS) for analyzing shift tables.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

ABBREVIATIONS

[redacted]	[redacted]
ABC-C	Aberrant Behavior Checklist-Community Edition
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice a day
C-SSRS	Columbia-Suicide Severity Rating Scale
CDKL5	cyclin-dependent kinase-like 5
CDD	CDKL5 deficiency syndrome
CGI-S	Clinical Global Impression of Severity
CH24H	cholesterol 24S-hydroxylase
CI	confidence interval
COVID-19	coronavirus disease 2019
CYP	cytochrome P450
DBP	diastolic blood pressure
DEE	developmental and epileptic encephalopathy
DMC	Data Monitoring Committee
DS	Dravet Syndrome
Dup15q	15q duplication syndrome
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EO	enzyme occupancy
ET	early termination
G-tube	gastrostomy tube
GCP	Good Clinical Practice
IB	investigator's brochure
ICF	informed consent form
INR	international normalized ratio
ITT	intention-to-treat
IDMC	independent Data Monitoring Committee
J-tube	jejunostomy tube
LGS	Lennox-Gastaut Sydnrome
LLN	Lower limit of normal
LOCF	last observation carried forward
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OLE	open-label extension

PEG tube	percutaneous endoscopic gastrostomy tube
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term (MedDRA)
Q1	25th percentile
Q3	75th percentile
QoLCE	Quality of Life in Childhood Epilepsy
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	standard of care
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	Upper limit of normal
VABS	Vineland Adaptive Behavior Scale
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective of this study is to assess the long-term safety and tolerability of soticlestat when administered as adjunctive therapy to at least one anti-seizure therapy (ie, antiepileptic drugs [AEDs], vagal nerve stimulator, ketogenic diet, or modified Atkins diet) in subjects with rare epilepsies.

1.1.2 Secondary Objective(s)

The secondary objectives, in subjects receiving soticlestat as adjunctive therapy to at least one anti-seizure therapy, are the following:

- *To assess the effect of soticlestat on seizure frequency.*
- *To assess the effect of soticlestat on the Clinical Global Impression of Severity (CGI-S) provided by the investigator.*

1.1.3 Additional Objective(s)

1.1.3.1 Exploratory Objective

The exploratory objectives, in subjects receiving soticlestat as adjunctive therapy to at least one anti-seizure therapy, are the following:

- *To assess the quality of life.*
- *To assess sleep disruption.*
- [redacted]
- [redacted]
- [redacted]

1.2 Endpoints

1.2.1 Primary Endpoint(s) – (Safety)

The primary endpoints (safety) include the following:

- *Incidence of* adverse events (AEs).
- *Change from Baseline in behavioral and adaptive functional measures using the Vineland Adaptive Behavior Scale (VABS).*
- *Change from Baseline in behavior measures using total scores and subscale scores of the Aberrant Behavior Checklist-Community Edition (ABC-C) for subjects ≥6 years of age.*
- *Change from Baseline in the Columbia-Suicide Severity Rating Scale (C-SSRS) categorization based on Columbia Classification Algorithm of Suicide Assessment categories 1, 2, 3, 4, and 5 for subjects ≥6 years of age.*

- *Absolute values and change from Baseline in clinical laboratory assessments, vital sign measurements, body weight, and electrocardiogram (ECG) parameters.*
- *Incidence of potentially clinically significant clinical safety laboratory test values, vital signs, weight, height, and ECG evaluations.*

1.2.2 Secondary Endpoint(s)

The secondary endpoints (efficacy) include the following:

- *Percent change from Baseline in all seizure 28-day frequency.*
- *Percent change from Baseline in drop seizure 28-day frequency (LGS subjects).*
- *Percent change from Baseline in convulsive seizure 28-day frequency (DS subjects).*
- *Percent change from Baseline in motor seizure 28-day frequency.*
- *Change from Baseline in CGI-S.*

1.2.3 Exploratory Endpoints

- *Change from Baseline in overall Quality of Life Childhood Epilepsy score (pediatric subjects).*
- *Change from Baseline in the Sleep Disruption Numerical Rating Scale.*
- [redacted]
- [redacted]
- [redacted]

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a multisite, OLE study designed to obtain additional safety and tolerability data related to soticlestat administered long-term in subjects with DEEs who participated in a previous soticlestat clinical study. Additional aims are to explore the long-term effects of soticlestat on seizure frequency and to assess the effects of soticlestat on quality-of-life measures.

Subjects will be eligible to enroll in this study within 15 days of completing the antecedent soticlestat study, except for adult subjects enrolled in the TAK-935-2001 study who will be eligible to enroll in this study up to 15 months after completion of the TAK-935-2001 study. In this OLE study, adults are defined as subjects who are 18 years or older.

A subject who completes the antecedent study between approximately 15 and 30 days before the Screening Visit can be enrolled in this study with the approval of the sponsor after considering the subject's overall compliance and after the subject meets all inclusion and no exclusion criteria for this study.

Approximately 160 subjects from several antecedent studies will be rolled over into this study. Table 2.a summarizes the antecedent TAK-935 studies included for this OLE study.

Subjects will receive soticlestat (BID) orally with or without food or via gastrostomy tube (G-tube) or percutaneous endoscopic gastrostomy (PEG) tube. A jejunostomy tube (J-tube) may be considered following approval by the sponsor and medical monitor. Subjects enrolled in clinical sites in China are not to receive study drug via G-tube, PEG tube, or J-tube. The planned doses of soticlestat represent the intended therapeutic doses of soticlestat and include the full range of doses available for soticlestat. Details of the dosing and titration schedules, including instructions for tapering doses of soticlestat after completion of treatment, are presented in Section 8.2 in the study protocol.

The Schedule of Study Procedures is presented by visit in Appendix A in the study protocol *and study procedures are presented in detail in Section 9.0* in the study protocol. *The Screening/Baseline visit may occur on the same day as the end of treatment visit of the antecedent study or within 30 days after the end of treatment visit of the antecedent study. Identical assessments taken at the subject's last visit of the antecedent study do not need to be repeated at Visit 1 of this study if these 2 visits are ≤30 days apart. After Visit 1, subsequent visits will occur at Weeks 1 (Day 1), 4, 12, 24, 36, 48 (all in Year 1); every 13 weeks starting with Week 65 in Years 2 and 3 and every 26 weeks thereafter.*

Starting from Year 4, visits will occur every 26 weeks, with every other visit (Visit 16, 18, 20, etc.) will be being conducted virtually. Scheduled virtual visits could be turned into onsite visits if requested by the parent/caregiver or the subject and/or deemed necessary by the investigator or the parent/caregiver or the subject.

In jurisdictions where home visits by site staff in clinical trials are allowed, these may be used as an alternative to study visits (onsite or virtual).

Safety, efficacy, and exploratory assessments will be performed at scheduled visits throughout the treatment period. AEs and concomitant medications will be monitored continuously throughout the study. [redacted]

The end of the study for an individual subject is defined as the last protocol-specified contact with that subject. The overall end of the study is defined as the last protocol-specified contact with the last subject ongoing in the study.

Table 2.a Antecedent TAK-935 studies included in this OLE study

Study	Brief Summary of Design	Population and treatment arms	Seizure Types	Comments
ARCADE TAK-935-18002	A multicenter, open-label, 2-cohort study in patients aged ≥2 and ≤35 years with 15q duplication syndrome (Dup15q) or CDKL5 deficiency disorder (CDD) demonstrating ≥3 motor seizures per month during the 3 months immediately prior to Screening.	A total of 20 patients with Dup15q or CDD (12 patients with CDD and 8 patients with Dup15q) were enrolled. This was a single arm study. Following a 4- to 6-week screening/baseline period, patients were treated with soticlestat up to 300 mg BID (weight-based dosing for patients weighing <60 kg) for up to 20 weeks (dose titration & optimization for 8 weeks and maintenance for 12 weeks), based on tolerability.	Motor seizures include hemiclonic, focal with motor signs, focal to bilateral tonic clonic convulsion, generalized tonic clonic convulsion, tonic, atonic, bilateral clonic, convulsive status (greater than 30 min)	All patients from the ARCADE study who rolled over to this OLE study did so within 15 days of completing the study.
ELEKTRA TAK-935-2002	Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study in pediatric patients (aged ≥2 and ≤17 years) with DS and LGS demonstrating ≥3 convulsive or ≥4 drop seizures, respectively, per month during the 3 months immediately prior to Screening (based on historical information) and ≥3 convulsive or ≥4 drop seizures, respectively, during a minimum of 4 weeks during the prospective Baseline Period (based on the seizure diary records).	A total of 141 patients (51 DS patients [26 soticlestat/25 placebo] and 90 LGS patients [45 soticlestat/45 placebo]) were randomized. Randomization was stratified by disease type (DS or LGS). Following a 4- to 6-week screening/baseline period, eligible patients were randomized to receive soticlestat or placebo up to 300 mg BID (weight-based dosing for patients weighing <60 kg) for up to 20 weeks (dose titration & optimization for 8 weeks and double blind maintenance for 12 weeks), based on tolerability.	Convulsive seizures include hemiclonic, focal to bilateral tonic clonic convulsion, generalized tonic clonic convulsion, bilateral clonic, and convulsive status > 30 minutes. Drop seizures include hemiclonic drop, focal with motor signs drop, focal to bilateral tonic clonic convulsion drop, generalized tonic clonic convulsion drop, absence or atypical absence drop, myoclonic drop, tonic drop, atonic drop, bilateral clonic drop, infantile spasms (if under 3 years of age) drop, epileptic spasms (if 3 years of age or older) drop, non-convulsive status (greater than 30 min) drop, convulsive status (greater than 30 minutes) drop.	All patients from the ELEKTRA study who rolled over to this OLE study did so within 15 days of completing the study.

Table 2.a Antecedent TAK-935 studies included in this OLE study

TAK-935-2001	Phase 1b/2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study with an open-label part designed to examine the safety, tolerability, PK, and PD of TAK-935 as adjunctive therapy in adult subjects with a diagnosis of developmental and/or epileptic encephalopathies (DEEs).	A total of 18 adult subjects (aged ≥18 and ≤65 years) with DEE demonstrating bilateral motor seizures (ie, drop seizures, tonicclonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonicclonic, focal seizures with bilateral hyperkinetic motor features) (average of ≥2 per month during the past 3 months) based on the investigator's assessment were enrolled. Following a 4- to 6-week screening/baseline period, eligible patients were randomized to receive soticlestat 100 mg BID or placebo for 10 days, then up to 200 mg BID or placebo for 10 days, then up to 300 mg BID or placebo for 10 days during the double-blind treatment period (part 1), based on tolerability. In Part 2, the open label maintenance phase, patients received soticlestat 200 mg BID for 10 days, then up to 300 mg BID for 44 days, based on tolerability.	Convulsive seizures include hemiclonic, focal to bilateral tonic clonic convulsion, generalized tonic clonic convulsion, bilateral clonic, convulsive status (greater than 30 min) Drop seizures include hemiclonic drop, focal with motor signs drop, focal to bilateral tonic clonic convulsion drop, generalized tonic clonic convulsion drop, absence or atypical absence drop, myoclonic drop, tonic drop, atonic drop, bilateral clonic drop, infantile spasms (if under 3 years of age) drop, epileptic spasms (if 3 years of age and older) drop, non convulsive status (greater than 30 min) drop, convulsive status (greater than 30 min) drop Motor seizures include: hemiclonic, focal with motor signs, focal to bilateral tonic clonic convulsion, generalized tonic clonic convulsion, tonic, atonic, bilateral clonic, convulsive status (greater than 30 min).	One patient from study TAK-935-2001 who rolled over to this OLE study did so within 15 days of completing the study. The remaining patients who rolled over to this OLE study did so more than 15 days after completing study TAK935-2001 and underwent a new 4-week baseline seizure diary assessment prior to receiving study treatment in the OLE study.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable. There is no formal hypothesis testing in this study.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

No formal sample size calculation has been performed for this extension study. A study size of approximately 160 subjects is based on the estimated number of subjects expected to enroll from the antecedent soticlestat studies (ARCADE/TAK-935-18-002, ELEKTRA/TAK-935-2002, and TAK-935-2001).

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

All enrolled subjects who take at least 1 dose of study medication in this study will be included in the safety analysis set. The safety set will be the primary population for all safety analyses.

5.2 Intent-to-Treat Analysis Set

All enrolled subjects will be included in the intent-to-treat analysis set.

5.3 Modified Intent-to-Treat Analysis Set

All enrolled subjects who have received at least 1 dose of study drug and have been assessed for seizures *for at least 1 day in the treatment period will be included in the modified intent-to-treat analysis set.*

The mITT analysis set will be used for all efficacy analyses.

5.4 [redacted]

[redacted]

5.5 [redacted]

[redacted]

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Unless otherwise specified, variables will be summarized descriptively by study visit. For categorical variables, the count (n) and percent (%) will be displayed. Unless otherwise stated, the denominator for percentages is the number of subjects in the relevant analysis set. For any summary by subgroups (e.g., by sex), the denominator is the number of subjects in that subgroup/treatment group within that analysis set, as applicable. Generally, "Missing" will be displayed as a category to represent missing data, where applicable. If missing is not a category, then the denominator is the number of subjects with non-missing values. For continuous variables, the number of subjects with non-missing values, mean, median, SD, Q1, Q3, minimum, and maximum values will be tabulated.

All log transformations will be based on natural logarithms.

Means and medians will be presented to 1 more decimal place than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data. Confident intervals (CIs) will be presented using the same number of decimal places as the parameter estimate.

Descriptive summaries for efficacy, safety, [redacted] endpoints will be provided by the following group, unless indicated otherwise.

Table 6.1.a Grouping Rules for Endpoints

Endpoints	Antecedent Studies			
	TAK-935-18002 (ARCADE)	**TAK-935-2001**	**TAK-935-2002 (ELEKTRA)**	**All Studies**
Disposition, Demographics and Baseline	Dup15q CDD	DEE	DS (Placebo, TAK-935, All) LGS (Placebo, TAK-935, All)	Overall
Efficacy (seizure only)	Dup15q CDD **Seizure types:** All, Motor Seizure	DEE **Seizure types:** All	DS **Seizure types:** All, Convulsive Seizure LGS **Seizure types:** All, Drop Seizure	Overall (only for All Seizures)
Efficacy (non-seizure endpoints: CGI-S, QOLCE, SDNRS etc.)	Dup15q CDD	DEE	DS, LGS	Overall
Medical History, Conmeds	Dup15q CDD	DEE	DS, LGS	Overall

Table 6.1.a Grouping Rules for Endpoints

Safety (AE, labs, ECG, Vitals, C-SSRS, Ophthalmological Examination, VABS etc.)	Dup15q CDD	DEE	DS, LGS	Overall
Potentially clinically significant clinical safety laboratory test values, vital signs, weight, height, and ECG evaluations	Dup15q CDD	DEE	DS, LGS	Overall
[redacted]				
Extent of exposure	Dup15q CDD	DEE	DS, LGS	Overall
Compliance				Overall

6.1.1 Handling of Treatment Misallocations

Not applicable.

6.2 Disposition of Subjects

The following summaries will be provided based on the ITT analysis set:

- The summary for study disposition including count/percentage of participants who have completed the study vs. count/percentage of participants who have prematurely withdrawn from the study, as well as the primary reasons for withdrawal.
- Summary of treatment discontinuation by visit window (Visit 1-4; Visit 4-5; and every 26 weeks from thereafter), reasons of withdraw (by categories listed in EDC).
- Other summaries:
  - Number of subjects enrolled by country, and site.
  - Analysis sets.
  - Significant protocol deviations.

A separate summary of disposition may be presented for patients whose participation of the trial is affected by COVID-19 in anyway (visit schedule, discontinuation, etc.).

All protocol deviations will be listed. A separate listing will be created for protocol deviations due to COVID-19 and a listing of visits affected by COVID-19 will be presented.

Patients excluded from the ITT, mITT and safety analysis sets will be listed.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Patient demographics (based on antecedent study) will be summarized and listed using the safety analysis set.

Demographic variables will include:

- Age.
- Age Categories [children [2-5 years], children [6-11 years], adolescents [12-17 years] and adults [18-64 years]).
- Sex.
- Ethnicity.
- Race.
- Country.

6.3.2 Baseline Characteristics

Baseline characteristics will be summarized and listed using the safety analysis set. Variables to be presented include:

- Height (cm).
- Weight (kg).
- Body mass index (BMI (kg/m2)).
- Number of AEDs taken per subject categorized as 0, 1, 2, 3 etc.
- Convulsive seizure frequency during Baseline Period (DS).
- Drop seizure frequency during Baseline Period (LGS).
- All seizure frequency during Baseline Period (All subjects).

For baseline definitions, please refer to Section 9.2.2

6.3.3 Medical History and Concurrent Medical Conditions

Medical history will be coded with MedDRA and will be summarized and listed by system organ class (SOC) and preferred terms. The actual version of the MedDRA coding dictionary will be noted in the clinical study report. The summary will include number and percentages of subjects. SOCs will be sorted in alphabetical order, while preferred terms will be sorted in decreasing frequency based on the total number of subjects. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms.

Summary of medical history will be based on the Safety Analysis Set.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

Any medication stopped prior to administration of first dose of study drug in this OLE study will be considered prior medication.

Prior medications will be coded with World Health Organization Drug Dictionary Enhanced and summarized by WHO drug Anatomic Therapeutic Chemical (ATC) class level 4 and preferred terms. Prior and concomitant medications will be listed, and prior medications will be flagged.

Prior medications will be summarized by ATC class level 2, ATC class level 4, and preferred term. In addition, prior AEDs will be summarized by ATC level 4 and preferred terms.

6.4.2 Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. A by-subject listing of concomitant medications will include all medications taken during the study regardless of the timing for the start of the medication. All medications stopped prior to the administration of the study drug will be included in the data but will be identified as prior in the listing. Only the concomitant medication use will be summarized.

The number and percentage of subjects who took at least 1 medication during treatment as well as the number and percentage of subjects who took each type of medication will be presented. Medications will be presented according to their WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) class level 4 and preferred drug name within ATC class level 4 by decreasing frequency of incidence for all groups combined.

Prior and concomitant medications will be listed with prior medications flagged. Similarly, prior and concomitant AEDs will be listed with prior medications flagged.

Concomitant medications will be summarized by ATC class level 2, ATC class level 4, and preferred term. Concomitant AEDs will also be summarized separately ATC class level 4, and preferred term.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint(s) Analysis

All primary endpoints are listed under safety. Please refer to Section 6.6.

6.5.2 Secondary Endpoint(s) Analysis

Descriptive statistics such as N, mean, median, SD, Q1, Q3, minimum, maximum etc. will be provided for continuous endpoints. For change from baseline and percent change from baseline, median and distribution free confidence intervals (CIs) based on ranks will be provided, if deemed necessary. Proc univariate with CIPCTLDF option in SAS may be used to obtain the CIs.

6.5.2.1 Secondary Endpoint(s) Analysis: Percent change from Baseline in all, drop (LGS only), convulsive (DS only) and motor seizure 28-day frequency.

Subjects rolling over from TAK-935-2001 were adults diagnosed with DEEs. For these subjects, percent change from baseline in total seizure frequency per 28 days will be summarized for each 12-week period starting from the date of first dose of study drug.

Subjects rolling over from TAK-935-2002 were children diagnosed with DS or LGS. For these subjects, percent change from baseline in convulsive seizure frequency per 28 days (DS only), drop seizure frequency per 28 days (LGS only), and total seizure frequency per 28 days will be summarized for each 12-week period starting from the date of first dose of study drug.

Subjects rolling over from TAK-935-18-002 were patients diagnosed with Dup15q or CDD. For these subjects, percent change from baseline in motor seizure frequency per 28 days and total seizure frequency per 28 days will be summarized for each 12-week period starting from the date of first dose of study drug.

Seizure frequency will be calculated for all seizures and by syndrome and seizure types of drop, convulsive and motor subtypes*.

***Convulsive seizures (DS only) include:**

- Hemiclonic (A).
- Focal to Bilateral Tonic Clonic Convulsion (D).
- Generalized Tonic Clonic Convulsion (E).
- Bilateral Clonic (J).
- Convulsive Status (Greater Than 30 Min) (N).

***Drop seizures (LGS only) include:**

- Hemiclonic Drop (AX).
- Focal with motor signs drop (CX).
- Focal to bilateral tonic clonic convulsion drop (DX).
- Generalized tonic clonic convulsion drop (EX).
- Absence or atypical absence drop (FX).
- Myoclonic drop (GX).
- Tonic drop (HX).
- Atonic drop (IX).
- Bilateral clonic drop (JX).
- Infantile spasms (if under 3 years of age) drop (KX).
- Epileptic spasms (if 3 years of age and older) drop (LX).
- Non convulsive status (greater than 30 min) drop (MX).
- Convulsive Status (Greater than 30 min drop) (NX).
- Other drop (OX).

***Motor seizures (Dup15q or CDD) include:**

- Hemiclonic (A).
- Focal with motor signs (C).
- Focal to Bilateral Tonic Clonic Convulsion (D).
- Generalized Tonic Clonic Convulsion (E).
- Tonic (H).
- Atonic (I).
- Bilateral Clonic (J).
- Infantile spasms (if under 3 years of age) (K).
- Epileptic spasms (if 3 years of age or older) (L).
- Convulsive Status (Greater Than 30 Min) (N).

The seizure frequency per 28 days during a specified interval of time and a specified set of seizure types (e.g. convulsive, drop, motor, all etc.) will be calculated as follows:

$$\left(\frac{\text{The total number of seizures of the specified type(s) counted in the seizure diary in the specified interval}}{\text{The total number of days seizure diary data is available in the specified interval}}\right) \times 28$$

If a subject has seizure data missing for more than 8 weeks in any 12-weeks of assessment interval, the subject will not be included in the analysis. Note that the denominator is same for all types of seizures for a specified interval of time for a given subject.

Descriptive summaries for percent change from baseline at each visit (eg, 12-week interval) in seizure frequencies will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Descriptive statistics for observed seizure frequencies for each time interval will also be provided (without CIs).

For subjects who enrolled in the OLE study ⩽15 days after completing the antecedent study, baseline seizure frequency is the baseline of the antecedent study. For subjects who rolled over to the OLE study >15 days after completing the antecedent study, baseline seizure frequency is
based on the prospective screening/baseline period of the OLE study. Please refer to Section 9.2.2.

In addition, line graphs plotting percent change from baseline in seizure frequency will be provided, with x-axis as time intervals (e.g., every 12 weeks during this OLE study), y-axis as percent change from baseline of seizure frequency.

A listing including patient identifier, visit, study day, seizure frequency, percent change from baseline in seizure frequency will be provided.

6.5.2.2 Secondary Endpoint(s) Analysis: Change from Baseline in CGI-S

The Clinician's Clinical Global Impression of Severity (CGI-S) is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (among the most severely ill patients). A score of 0 may be recorded on the case report form (CRF), indicating "not assessed"; this score will be treated as missing for the calculation of descriptive statistics.

The count and percentage of each category will be provided by visit. In addition, the number and percentage of subjects with improvement from baseline by at least 1 point/category (change from baseline <= -1) will be presented by visits and groups specified in Table 6.1.a.

6.5.3 Exploratory Endpoints Analysis

Descriptive statistics such as mean, median, SD, Q1, Q3, minimum, maximum etc. will be provided for continuous endpoints. No CIs will be provided unless otherwise specified.

6.5.3.1 Change from Baseline in overall Quality of Life Childhood Epilepsy score (pediatric subjects)

The Quality of Life in Childhood Epilepsy (QOLCE) is a parent-reported questionnaire that evaluates health-related quality of life in children ages 4 to 18 years old. It contains 76 items with 16 subscales covering 7 domains of life function: physical activities, social activities, cognition, emotional wellbeing, behavior, general health, and general quality of life. This scale will only be used for pediatric patients. All scale scores in the QOLCE were transformed linearly into scales of 0-100 points (values = 0, 25, 50, 75, 100), with higher scores representing better quality of life. "Not applicable" responses to any question were coded as missing values. The overall scores will be calculated as unweighted mean of 16 subscale scores (shown in the table below). The subscale scores can be calculated as the sum of items in each subscale divided by number of items in each subscale that the respondent answered in that subscale. If any of the subscales is completely missing, the denominator for unweighted mean will be less than 16 (subtracting the missing ones from 16). If more than 7 subscales are missing, the overall score will be set to missing.

Subscale	Question #
Physical Restrictions	1-10
Energy/Fatigue	11-12
Attention/Concentration	13-17
Memory	18-23
Language	24-31
Other Cognitive	32-34
Depression	35-38
Anxiety	39-44
Control/Helplessness	45-48
Self Esteem	49-53
Social Interactions	54-56
Social Activities	57-59
Stigma Item	60

Subscale	Question #
Behavior	61-74
General Health	75
Quality of Life	76

The change from baseline in overall Quality of Life Childhood Epilepsy score (QOLCE) will be summarized descriptively as a continuous variable.

6.5.3.2 Change from Baseline in the Sleep Disruption Numerical Rating Scale

The patient's caregiver will be asked: "On a scale of '0 to 10', please circle the number that best describes your child's sleep disruption in the last week." The markers range from 0 (slept extremely well) to 10 (unable to sleep at all). If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within 3 days.

The change from baseline in the Sleep Disruption Numerical Rating Scale (SDNRS) will be summarized descriptively as a continuous variable over time.

6.5.3.3 [redacted]

[redacted].

6.5.3.4 [redacted]

[redacted]

6.5.3.5 [redacted]

[redacted]

6.5.4 Subgroup Analyses (if applicable)

Not applicable.

6.6 Safety Analysis

Descriptive statistics will be used to summarize all safety endpoints. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital sign measurements, body weight, ECG parameters, as well as changes in behavioral and adaptive functioning measures using VABS and subscales of ABC-C. Changes from Baseline to study timepoints in clinical chemistry and hematology results will be summarized descriptively. Each laboratory parameter will be classified as low, normal, or high relative to the parameter's reference range. The number and percentage of subjects with shifts in clinical

laboratory parameters will be summarized. Laboratory abnormalities will also be summarized with shift tables, if deemed appropriate and necessary. Listings of subjects with abnormal results will be provided.

6.6.1 Adverse Events

Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term (PT) and system organ class (SOC) categories. Serious AEs and AEs leading to study discontinuation will also be summarized.

The following definitions will be used for AEs:

- *Treatment-emergent AE (TEAE): Any AE that starts or increases in severity during or after the first dose of study drug.*
- *Treatment-emergent SAE: A TEAE that is serious.*

The incidence of TEAEs, discontinuations due to TEAEs, drug-related, serious, and severe TEAEs will be summarized. Detailed listings of AEs, SAEs, related AEs, and discontinuations due to AEs will be provided.

All data will be listed by subject.

When calculating the frequency and percentage of subjects who reported AEs, a subject will be counted only once for each SOC or PT when multiple AEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple AEs coded to the same SOC or PT, the AE with maximum intensity or strongest relationship will be included in the summary.

AEs with missing intensity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. If the relationship of an event is missing, the relationship for the event will be considered to have been related.

AE dates that are partially or completely missing will be presented as they are in the listings, although incomplete adverse event (AE) start dates will be imputed to determine the relationship between the start date and the informed consent date, as well as the start date and the first dose date of the study (except when the event end date was prior to the study drug start date).

The following methods will be used to impute incomplete start dates of AEs:

- If only the month and year of the start date are available and the month and year are different than the month and year of the first dose of double-blind study medication or the stop date is prior to the first dose of study medication, then the first day of the month will be used for the start date. If only the month and year of the start date are available and the month and year are the same as the month and year of the first dose of double-blind study medication and the stop date is not prior to the date of first dose, then the date of first dose will be used for the start date.
- If only the year of the start date is available and the year is different than the year of the first dose of double-blind study medication or the stop date is prior to the first dose of study medication, then January 1st will be used for start date. If only the year of the start date is available and the year is the same as the year of the first dose of double-blind study

  medication and the stop date is not prior to the date of first dose, then the date of first dose will be used for start date.

In general, AEs will be tabulated by group specified in Table 6.1.a. The summary tables will include the number and percentage [n (%)] of subjects. The tables will include number of events. Summary tables that will be generated will include, but may not be limited to:

- Overall TEAEs
- TEAEs by SOC and PT
- Frequently occurring (≥ 5% of all subjects) TEAEs by PT (the 5% cut-off value will be applied to total before rounding)
- TEAEs by Maximum Severity, SOC and PT
- Drug-Related TEAEs by SOC and PT
- TEAEs leading to Discontinuation by SOC and PT
- Serious TEAEs by SOC and PT
- Non-serious TEAEs by SOC and PT
- Relationship of TEAEs to Study Drug by SOC and PT
- Serious Drug-Related TEAEs by SOC and PT

Data listings will be provided for TEAEs, TEAEs leading to study drug discontinuation, SAEs, and TEAEs that resulted in death.

In addition, a list of AEs in subjects with concomitant perampanel will be provided.

6.6.2 Other Safety Analysis

6.6.2.1 Change from Baseline in behavioral and adaptive functional measures using the Vineland Adaptive Behavior Scale (VABS)

The Vineland Adaptive Behavior Scale, 3rd Edition, Comprehensive Parent Caregiver Form (VABS-3 Parent Caregiver Form), is a caregiver-report questionnaire that assesses adaptive functioning across 4 domains and 11 subdomains.

Domain	**Subdomains**
Communication	Listening and Understanding Talking Reading and Writing
Daily Living	Caring for Self Caring for Home Living in the Community
Social Skills and Relationships	Relating to Others Playing and Using Leisure Time Adapting
Problem Behaviors	Section A Section B Section C

Each item is scored from 0 to 2. If a caregiver estimates a response, the item score is reported as 97, 98, or 99 on the CRF to indicate that they are estimates, but for the calculation of domain and subdomain totals, 97 is mapped to 2, 98 is mapped to 1 and 99 is mapped to 0. For each subdomain in the table above, the total raw scores will be calculated.

Change from baseline in subdomain total raw scores will be analyzed descriptively as a continuous variable over time.

6.6.2.2 Change from Baseline in behavior measures using total scores and subscale scores of the Aberrant Behavior Checklist-Community Edition (ABC-C) for subjects ≥6 years of age

The ABC-C measures psychiatric symptoms and behavioral disturbance exhibited by individuals across 5 subscales with 58 items: irritability, agitation, and crying (Irritability subscale: 15 items); lethargy, social withdrawal (Lethargy/Social Withdrawal subscale: 16 items); stereotypy (Stereotypic Behavior subscale: 7 items); hyperactivity/noncompliance (Hyperactivity subscale: 16 items); and inappropriate speech (Inappropriate Speech subscale: 4 items). Each item is rated on a scale of 0 to 3 ("not at all a problem" to "the problem is severe in degree").

The scale includes 5 subscales with the sub scores derivation. The total score is calculated by summing the scores on all 58 items. Each subscale score is calculated by summing the items below. The ABC-C total score will be calculated only when all associated subscales scores are derived and not missing.

SUBSCALES	**Sum of Questions**
Irritability	2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57
Lethargy/Social Withdrawal	3, 5, 12, 16, 20, 23, 26, 30, 32, 37, 40, 42, 43, 53, 55, 58
Stereotypic Behavior	6, 11, 17, 27, 35, 45, 49
Hyperactivity	1, 7, 13, 15, 18, 21, 24, 28, 31, 38, 39, 44, 48, 51, 54, 56
Inappropriate speech	9, 22, 33, 46

Change from baseline in ABC-C total and subscale scores will be summarized descriptively as a continuous variable.

For ABC-C, the maximum amount of missing data that can be acceptable varies by subscale. The following upper limits of missing items tolerated for each subscale: (I) Irritability (15-item scale): 3 items; (II) Lethargy/Social Withdrawal (16-item scale): 3 items; (III) Stereotypic Behavior (7-item scale)" 2 items; (IV) Hyperactivity/Noncompliance (16-item scale): 3 items; (V) Inappropriate Speech (4-item scale): 1 item. If more items than the stated upper limit have been left blank (unscored) by the rater, then the associated subscale will not be computed at all and will be set to missing.

When the amount of missing data is within specified limit, the subscale scores will be prorated as follows:

(a) Take the total number of items on the subscale and divide this by the number of completed items. This will result in a number larger than 1.00. (b) Multiply that number by the total score for that subscale. (c) This becomes the new total score for this subscale for the given subject. For example, values of 13 items out of 15 Irritability questions are applicable with a sum of 23, then the prorated score of Irritability is (15/13) *23=26.54.

The ABC-C total score will be calculated only when all associated subscales scores are derived and not missing.

6.6.2.3 Change from Baseline in the Columbia-Suicide Severity Rating Scale (C-SSRS) categorization based on Columbia Classification Algorithm of Suicide Assessment categories 1, 2, 3, 4, and 5 for subjects ⩾6 years of age.

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be obtained from the questionnaires.

Responses to questions in the Columbia-Suicide Severity Rating Scale (C-SSRS) and change in responses from baseline (using shift tables) at each post-baseline collection time point will be summarized descriptively for patients ≥6 years of age. Summaries will be based the SUICIDAL IDEATION part (Questions 1, 2, 3, 4, and 5) and the SUICIDAL BEHAVIOR part (Questions on Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Actors or Behavior, Suicidal Behavior, and Completed Suicide. The number and percentages of response to each question (Yes) will be summarized over time.

C-SSRS incidences will be categorized as follows: no suicidal ideation or suicidal behavior or non-suicidal self-injurious behavior, non-suicidal self-injurious behavior, suicidal ideation, and suicidal behavior. For each visit, the "Yes" answer to the question with the highest severity rank in Table 6.6.a will be used to determine the C-SSRS category of a subject.

Table 6.6.a Severity Rank for C-SSRS Questions

C-SSRS Categories	Severity Rank of CSSRS questions (from low to high)
Non-suicidal self-injurious behavior	1. Engaged in non-suicidal self-Injurious behavior
Suicidal ideation	2. Wish to be dead
	3. Non-specific active suicidal thoughts
	4. Active suicidal ideation with any methods (not plan) without intent to act
	5. Active suicidal ideation with some intent to act, without specific plan
	6. Active suicidal ideation with specific plan and intent
Suicidal behavior	7. Preparatory acts or behavior
	8. Aborted attempt
	9. Interrupted attempt
	10. Actual attempt
	11. Completed suicide (only applicable for the postbaseline assessments)

The number and percentage of subjects with suicidal ideation, suicidal behavior, and the number and percentage of subjects who have "Yes" answers of the suicidal ideation and behavior questions will be summarized by visit.

Shifts in C-SSRS will be presented as cross-tabulation (baseline versus post-baseline categories as in Table 6.6.a) of numbers and percentages of subjects of no suicidal ideation or suicidal behavior or non-suicidal self-injurious behavior, non-suicidal self-injurious behavior, suicidal ideation, suicidal behavior, and total by visit.

Note that subjects less than 6 years of age at the start of antecedent studies will have missing baseline.

The summaries will be presented by group specified in Table 6.1.a.

C-SSRS data will be listed.

6.6.2.4 Incidence of Potentially Clinically Significant Clinical Safety Laboratory Test Values, Vital Signs, Weight, Height, and ECG Evaluations

The potentially clinically significant safety values for this study are listed in the table below. These values have been chosen because they are widely accepted abnormalities (including weight, height, QTcF interval, liver function test results or Creatinine), or have been used as markedly abnormal values in previous Takeda studies (BUN and hemoglobulin), or haven been adjusted from edit check rules of soticlestat studies. and are all highly unlikely to be considered as not clinically significant.

Table 6.6.b Potentially Clinically Significant Values

Parameter	High	Low
SBP (2 to <8 years)	>137mmHg	<77mmHg
SBP (8 to <12 years)	>146mmHg	<80mmHg
SBP (≥12 years)	>160mmHg	<80mmHg
DBP (2 to <8 years)	>97mmHg	<40mmHg
DBP (8 to <12 years)	>100mmHg	<46mmHg
DBP (≥12 years)	>100mmHg	<50mmHg
Heart Rate (2 to <4 years)	>160bpm	<80bpm
Heart Rate (4 to <6 years)	>145bpm	<55bpm
Heart Rate (6 to <9 years)	>140bpm	<50bpm
Heart Rate (9 to <12 years)	>130bpm	<50bpm
Heart Rate (12 to <16 years)	>120bpm	<50bpm
Heart Rate (≥16 years)	>110bpm	<50bpm
QTcF	>500ms	NA
Height (in patients<18 years old)		Below -2SD for age and gender in WHO growth chart
Weight (in patients ≤10 years old)		Below -2SD for age and gender in WHO growth chart.
ALT or AST+TBiL	ALT/AST>3 × ULN+ TBiL>2 × ULN	NA
ALT or AST+INR	ALT/AST>3 × ULN+ INR>1.5	NA
ALT or AST	>5 ULN and persists for >2 weeks	NA
ALT or AST	>8 ULN	NA

Table 6.6.b Potentially Clinically Significant Values

Creatinine	>1.5ULN	NA
Blood urea nitrogen	>10.7 mmol/L	NA
Hemoglobin	>1.2 × ULN	<0.8 × LLN

NA = Not Applicable

The number and percentage of subjects with potentially clinically significant clinical safety values will be summarized by group specified in Table 6.1.a. for each parameter and reference range.

Additionally, a listing for all the potentially clinically significant safety parameters will be provided.

6.6.2.5 Change from baseline in safety laboratory test values, vital signs, and ECG evaluations.

Changes from Baseline to study timepoints in clinical chemistry and hematology results will be summarized descriptively.

Clinical laboratory tests will be evaluated and presented using International System of Units (SI) units unless otherwise stated. All laboratory test parameters will be displayed in individual subject data listings in both SI units and conventional (CV) units, if available. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets. All summaries and analyses will be based on the values using these preferred SI units.

Listings of all clinical safety laboratory data will be provided in both SI and CV (conventional units) units (if available and deemed necessary). Laboratory data outside of the normal reference range will be indicated in the listings. The listing will include site number, subject identifier, age, gender, study visit, and sample collection date.

Descriptive statistics for the observed and change from baseline values will be presented. Study baseline will be used for change from baseline. Measurements will be summarized by nominal timepoints.

Descriptive statistics will be used to summarize vital sign parameters (including systolic and diastolic blood pressure, heart rate, respiratory rate and temperature) at baseline, each postbaseline visit, and change from baseline to each post-baseline visit

Listings of all vital signs data will be provided. The listing will include site number, subject identifier, age, gender, study visit, and sample collection date.

Descriptive statistics of ECG parameters will be presented for baseline, each post-baseline visit, and change from baseline to each post-baseline visit.

Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each postbaseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations, and total categories, as applicable, by group specified in Table 6.1.a.

The number of subjects and corresponding percentages will be presented for each category defined below for each post-baseline timepoint. Post-baseline QTcF values will be categorized as: <450 msec, 450 msec – <480 msec, 480 msec – 500 msec, and > 500 msec. The change from baseline values (ΔQTcF) will be categorized as: <30 msec, 30 msec – 60 msec, and > 60 msec.

Listings of all 12-lead ECG data will be provided. The listing will include site number, subject identifier, age, gender, study visit, and sample collection date.

6.6.2.6 Ophthalmological Evaluations

Visual acuity, visual confrontations and fundoscopic examination in ophthalmological evaluations are collected in Case Report Forms (CRF).

The number and percentages of subjects having optic nerve exam as abnormal in fundoscopic examination and visual confrontations will be summarized by group (as per Table 6.1.a.) at baseline and at each post-baseline visits.

The change from baseline in the visual acuity left and right eye combined will be summarized descriptively as a continuous variable over time.

All ophthalmological evaluation data will be listed.

6.6.2.7 Neurological Examination

Neurological examination results will be summarized descriptively at each scheduled time point, by categories. The number and percentages of subjects with response as abnormal in each category will be provided over time including baseline. It will be presented by group (as per Table 6.1.a.)

All neurological examination data will be listed.

6.6.2.8 Physical Examination

Physical examinations will be summarized by number of subjects with abnormal finding as collected in CRF at baseline and each post-baseline visit. It will be presented by overall group only.

Physical examination data will also be listed.

6.6.2.9 Change from baseline in height and weight for all age groups,

The change from baseline for height and weight will be summarized descriptively by visit and age groups (Pediatrics: Age <18, Adults: Age >= 18 years) as a continuous variable. It will be presented by overall group only (as in Table 6.1.a).

6.6.3 Other Safety Analysis

To explore growth trends in weight and height, observed weights (or heights) for subjects 18 years old or younger will be analyzed using a linear mixed effects model with time of assessment (years since first dose) and baseline weight (or height) as continuous covariates. The model will use a random intercept and random slope in time that have an unstructured covariance matrix. Male and female subjects will be analyzed separately for these baseline age groups: Males 2-11, 12-15, 16-18 years; females 2-9, 10-13, 14-18 years. These age group were chosen based on different annual height and weight velocities from CDC growth chart for boys and girls (2-20 years)[12]. Restricted maximum likelihood estimates and standard errors for the fixed regression parameters will be presented for each age group, and results will be displayed graphically.

6.6.4 Extent of Exposure and Compliance

Extent of exposure (in days) of study medication is defined as (date of last dose – date of first dose +1)/7. Total actual dose is defined as the sum of actual doses (all non-missed doses are considered full dose).

- Total dose given, average daily dose, and duration of exposure (treatment duration in days) will be summarized (descriptive statistics such as N, mean, SD, median, minimum, and maximum) for all patients by group specified in Table 6.1.a.

- Median/range of treatment duration in the study for subjects who withdraw under each category will be provided.

In addition, number and percentage of subjects in each maintenance dose categories will be provided by dose level (dose 1. dose 2, dose 3 and others, if any). Maintenance dose is defined as the longest duration dose within the maintenance period. If there are multiple doses with the longest duration, the highest dose will be used as the maintenance dose.

The percentage of study drug compliance will be assessed in two ways:

1) Using the daily seizure and medication diary, as

$$\%Study\ Drug\ Compliance = \left(\frac{Dose\ Recorded\ as\ Taken}{Total\ Planned\ Dose}\right) \times 100\%$$

2) Using number of returned tablets,

$$\%Study\ Drug\ Compliance = \left(\frac{Dose\ Dispensed - Dose\ Returned}{Total\ Planned\ Dose}\right) \times 100\%$$

Total planned dose will be derived as the sum of the dose the subject supposed to take.

For each group and overall, study medication compliance will be summarized by compliance category (0 to <20%, 20% to <40%, 40% to <60%, 40% to <60%, 60% to <80%, 80% to <100%, 100% to <120% and ≥ 120%) and the number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for overall. In addition, Number, and percentage of subjects with seizure diary compliance will be summarized by <80% and >=80%.

Seizure diary compliance is assessed over the period starting from date of first dose and ending on the date of the End of Maintenance (or Early Termination) visit. Seizure diary compliance will be summarized in a similar fashion. Compliance is calculated as:

$$\left(\frac{\text{Number of days in this period with seizure diary data}}{\text{Total number of days in this period}}\right) \times 100\%$$

All study drug administration and compliance data will also be listed. All analyses will be performed using safety analysis set.

6.7 [redacted]

6.7.1 [redacted]

[redacted]

[redacted]

[redacted]

6.7.2 [redacted]

[redacted]

6.7.3 [redacted]

[redacted]

6.7.4 Other Analyses

Not applicable.

6.8 Interim Analyses

Interim data cuts from the ongoing study will be analyzed according to this Statistical Analysis Plan to support any regulatory submissions. Since there is no hypothesis testing involved, no interim analysis will require spending any type-I error.

6.9 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

An independent Data Monitoring Committee (DMC) will meet regularly to review unblinded clinical safety data. Details are provided in the DMC Charter.

7.0 REFERENCES

1. 2 to 20 years: Boys Stature Weight-for-age percentiles. https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf.May 30, 2000.

2. 2 to 20 years: Girls Stature Weight-for-age percentiles. https://www.cdc.gov/growthcharts/data/set1clinical/cj41l022.pdf.May 30, 2000.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Changes made from the previous version of the SAP that have a **material impact to the planned statistical analysis methods** are described below. In addition, there were textual changes purely to improve the flow, organization, and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

Table 9.1.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
5.3	All enrolled subjects who have received at least 1 dose of study drug and have been assessed for at least 1 day in the treatment period will be included in the modified intent-to-treat analysis set.	All enrolled subjects who have received at least 1 dose of study drug and have been assessed **for seizures** for at least 1 day in the treatment period will be included in the modified intent-to-treat analysis set.	Added "for seizures" for detailed clarification.
6.1 Table 6.1.a	NA. A row added to the table (Table 6.1.a).	Added row for potentially clinically significant clinical safety laboratory test values, vital signs, weight, height, and ECG evaluations.	To specify grouping rule for the summary table.
6.5.3.3	[redacted]	[redacted]	[redacted]

Table 9.1.a Summary of Changes in SAP

6.6.2.3	Shift table categories have been redefined.	Modify C-SSRS shift table categories. Refer to Table 6.6.a for details on categories.	Updated categories for shift tables allow more appropriate clinical interpretation.
6.6.2.4	NA	New section added with a definition of potentially clinically significant events. Refer to Table 6.6.b.	Details added to define potentially clinically significant events for clinical safety laboratory test values, vital signs, weight, height, and ECG evaluations, which is one of the primary safety endpoints.
6.6.2.6	Visual acuity, visual confrontations and fundoscopic examination in ophthalmological evaluations are collected in Case Report Forms (CRF). The number and percentages of subjects having optic nerve exam as abnormal in fundoscopic examination will be summarized by group (as per Table 6.1.a) at baseline and at each post-baseline visits. All ophthalmological evaluation data will be listed.	Visual acuity, visual confrontations and fundoscopic examination in ophthalmological evaluations are collected in Case Report Forms (CRF). The number and percentages of subjects having optic nerve exam as abnormal in fundoscopic examination and visual confrontations will be summarized by group (as per Table 6.1.a) at baseline and at each post-baseline visits. The change from baseline in the visual acuity left and	Added "Visual Confrontations" with other parameters to summarize by group at baseline and at each post-baseline visits. Added analysis for Visual Acuity for summary table.

Table 9.1.a Summary of Changes in SAP

		right eye combined will be summarized descriptively as a continuous variable over time. All ophthalmological evaluation data will be listed.	
6.6.3	NA	New section added. To explore growth trends in weight and height, observed weights (or heights) for subjects 18 years old or younger will be analyzed using a linear mixed effects model with time of assessment (years since first dose) and baseline weight (or height) as continuous covariates. The model will use a random intercept and random slope in time that have an unstructured covariance matrix. Male and female subjects will be analyzed separately for these baseline age groups: Males 2-11, 12-15, 16-18 years; females 2-9, 10-13, 14-18 years. These age group were chosen based on different annual height and weight velocities from CDC growth chart for boys and girls (2-20 years)[12]. Restricted maximum	To explore growth trends in observed heights and weights for subjects 18 years old or younger.

Table 9.1.a Summary of Changes in SAP

		likelihood estimates and standard errors for the fixed regression parameters will be presented for each age group, and results will be displayed graphically.	
6.6.4	In addition, number and percentage of subjects will be provided by dose level (1. 2. 3) **at each visit**. Using the **electronic** daily seizure and medication diary.	Updated content #1: In addition, number and percentage of subjects in each maintenance dose categories will be provided by dose level (dose 1. dose 2, dose 3 and others, if any). Maintenance dose is defined as the longest duration dose within the maintenance period. If there are multiple doses with the longest duration, the highest dose will be used as the maintenance dose. Updated content #2: Using the daily seizure and medication diary.	Updated the definition of maintenance dose and removed "by visit". Removed word "electronic" to align with protocol amendment 4.
6.7.2	[redacted]	[redacted]	[redacted]

Table 9.1.a Summary of Changes in SAP

		[redacted]	[redacted]
7.0	NA	Added References to support Section 6.6.3.	Added as reference.

Table 9.1.a Summary of Changes in SAP

9.2.2	*Baseline for analyses is the baseline of the antecedent study, except for subjects who completed the antecedent study >15 days before the Screening Visit of this study.* In this situation (> 15 days), the last non-missing assessment prior to the first dose in this study will be used in change/percent change from baseline analyses or shift analyses. For seizure frequency, the 4-week baseline period of this study will be used to compute the baseline frequency. Unless otherwise specified or the above situation (*>15 days)*, baseline is defined as the last non-missing assessment prior to the first dose of the antecedent studies, will be used in change/percent change from baseline analyses or shift analyses. For seizure frequency, the prospective 4 to 6- week baseline period of the antecedent study will be used to compute the baseline frequency.	*Baseline for analyses is the baseline of the antecedent study, except for subjects who completed the antecedent study >15 days before the Screening Visit of this study.* In this situation (> 15 days), the last non-missing assessment prior to the first dose in this study will be used in change/percent change from baseline analyses or shift analyses. For seizure frequency, the 4-week baseline period of this study will be used to compute the baseline frequency. Unless otherwise specified or the above situation (*>15 days)*, baseline is defined as the last non-missing assessment prior to the first dose of the antecedent studies, will be used in change/percent change from baseline analyses or shift analyses. For seizure frequency, the prospective 4 to 6- week baseline period of the antecedent study will be used to compute the baseline frequency. Added content: [redacted] For Visual Acuity, the earliest assessment from the antecedent studies will be	Clarification added.

Table 9.1.a Summary of Changes in SAP

		[redacted]	
9.2.3	Unless otherwise specified, **all the summary tables by visit will use the values from the scheduled visit. For scheduled visits, nominal visits will be used without any windowing.** A windowing convention using	Unless otherwise specified, A windowing convention using midpoint technique (using study days) will be used to determine the mapping of the data for all the visits regardless of	Updated for more clarity in visit windowing which is considered for all the visits regardless of

Table 9.1.a Summary of Changes in SAP

	midpoint technique (using study days) will be used to determine the mapping of the data **from unscheduled visits, as appropriate**. **Data from scheduled visits will be used for analysis even if there is data at an unscheduled visit that can be mapped to the same scheduled visit. When more than one result for a parameter is obtained in a visit window from unscheduled visits provided there is no data from the scheduled visit, the latest one will be used for analysis.**	scheduled or unscheduled visits.	scheduled and unscheduled. Removed second paragraph as all data will be used for mapping into the analysis visit windows. More details are provided in Section 9.2.4.
9.2.4	NA	Clarifying details added for rules to select a single record from multiple records in an analysis visit window.	Technical details added for clarification.

NA = Not Applicable

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

9.2.2 Definition of Baseline

Baseline for analyses is the baseline of the antecedent study, except for subjects who completed the antecedent study >15 days before the Screening Visit of this study.

In this situation (> 15 days), the last non-missing assessment prior to the first dose in this study will be used in change/percent change from baseline analyses or shift analyses. For seizure frequency, the 4-week baseline period of this study will be used to compute the baseline frequency.

Unless otherwise specified or the above situation (*>15 days)*, baseline is defined as the last non-missing assessment prior to the first dose of the antecedent studies, will be used in change/percent change from baseline analyses or shift analyses. For seizure frequency, the prospective 4 to 6- week baseline period of the antecedent study will be used to compute the baseline frequency.

For Visual Acuity, the earliest assessment from the antecedent studies will be considered as baseline for summary tables.

9.2.3 Definition of Visit Windows

Unless otherwise specified, A windowing convention using midpoint technique (using study days) will be used to determine the mapping of the data for all the visits regardless of scheduled or unscheduled visits.

9.2.4 Rules to select appropriate record from multiple assessments for summary tables

The rules provided below will be followed to select an assessment from an analysis visit window that has multiple assessments to report in the summary tables. If there are multiple records at visits (e.g. Scheduled, ET, Unscheduled) mapped into a particular analysis visit window, in general, the order of preference to select record for summary will be as follows: Scheduled, ET, Unscheduled.

Endpoints: Laboratory Values, Vital Signs and ECG Evaluations

When more than one result for a parameter is obtained in a visit window, the latest one will be used. If multiple measurements are recorded at the same time, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be used.

Endpoints: VABS, C-SSRS, ABC-C, CGI-S, Sleep Disruption and Quality of Life.

If multiple assessments occur in the same window, the assessment done at the scheduled visit will be mapped to the corresponding analysis visit. If only unscheduled visits are available, the assessment within the window and closest to the scheduled visit (i.e. the corresponding study day of the scheduled visit per latest protocol) will be used. If there are two unscheduled assessments within the window and they are equally close to the scheduled visit, the later assessment will be used.

9.3 Analysis Software

SAS System® Version 9.4 or higher will be used in the statistical analysis.

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