Statistical Analysis Plan

NCT Number: NCT06422377

Title: An Open-label, Nonrandomized, Phase 3 Study to Evaluate the Efficacy and Safety of Soticlestat in Participants With Dravet Syndrome or Lennox-Gastaut Syndrome Who Have Been Exposed to Fenfluramine.

Study Number: TAK-935-3004

Document Version and Date: Original, 27 June 2023

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-935-3004

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Phase 3

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original Version	See signature page	Not Applicable

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ASM	antiseizure medication
ATC	anatomic therapeutic chemical
BID	twice daily
BMI	Body mass index
Care GI-I	Caregiver Global Impression of Improvement
CGI-I	Clinical Global Impression of Improvement
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DS	Dravet syndrome
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EQ-VAS	visual analogue scale
ET	early termination
ITT	intention-to-treat
MMD	major motor drop
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OLE	open-label extension
PK	pharmacokinetic
PT	Preferred Term (MedDRA)
Q1	25th percentile
Q3	75th percentile
QI-Disability	Quality of Life Inventory-Disability
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOC	System Organ Class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To assess the efficacy of soticlestat in participants with DS or LGS who have been exposed to fenfluramine.

1.1.2 Additional Objectives

1.1.2.1 Exploratory Objectives

- *To explore effects of soticlestat on seizure frequency, quality of life and non-seizure symptoms in participants with DS or LGS who have been exposed to fenfluramine.*
- *To explore safety and tolerability of soticlestat in participants with DS or LGS who have been exposed to fenfluramine.*

1.2 Endpoints

1.2.1 Primary Endpoint(s)

- For DS cohort: Percent change from baseline in convulsive seizure frequency per 28 days during the initial 12 weeks of the maintenance period.
- For LGS cohort: Percent change from baseline in major motor drop (MDD) seizure frequency per 28 days during the initial 12 weeks of the maintenance period.

1.2.2 Exploratory Endpoints

- *Percent change from baseline in convulsive (DS)* or *MMD (LGS) seizure frequency per 28 days during every 12 weeks after the initial 12 weeks of the maintenance period.*
- *Percent change from baseline in convulsive (DS)* or *MMD (LGS) seizure frequency per 28 days during the initial 16 weeks of the treatment period (4 weeks of titration + initial 12 weeks of maintenance).*
- *Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 12 weeks of the maintenance period.*
- *Percent change from baseline in total seizure frequency per 28 days of all seizure types during every 12 weeks after the initial 12 weeks of the maintenance period.*
- *Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 16 weeks of the treatment period (4 weeks of titration + initial 12 weeks of maintenance).*

- *Percent change from baseline in seizure frequency per 28 days of each seizure type identified at the time of screening or baseline during the maintenance period and full treatment period (52 weeks).*
- *Treatment response as defined by ≥50% reduction in convulsive (DS)* or *MMD (LGS) seizure frequency per 28 days from baseline every 12 weeks after the initial 12 weeks of the maintenance period.*
- *Treatment response as defined by ≥50% reduction in convulsive (DS)* or *MMD (LGS) seizure frequency per 28 days from baseline during the initial 16 weeks of the full treatment period (4 weeks of titration period + 12 weeks of maintenance period).*
- *Clinical Global Impression of Improvement (CGI-I) (clinician).*
- *Caregiver Global Impression of Improvement (Care GI-I).*
- *CGI-I Seizure Intensity and Duration.*
- *CGI-I Non-seizure Symptoms completed by clinician with input from the caregivers.*
- *Quality of Life Inventory-Disability (QI-Disability).*
- *Change in EQ-5D 5-level version (EQ-5D-5L) and EQ-5D visual analogue scale (EQ VAS) scores.*
- *Caregiver satisfaction questionnaire.*
- *Days when rescue anti-seizure medication (ASM) is used.*

Safety Endpoints include

- *Incidence of treatment- emergent adverse events (TEAEs).*
- *Columbia-Suicide Severity Rating Scale (C-SSRS).*
- *Ophthalmological evaluations.*

1.3 Estimand(s)

1.3.1 Primary Estimand

Since this is a descriptive study, an estimand framework is not necessary.

2.0 STUDY DESIGN

2.1 Overall Study Design

This is a phase 3, open-label, nonrandomized, single-arm study in participants with DS or LGS who have been exposed to fenfluramine.

"Exposure" is defined as participants who are current or prior users of fenfluramine.

Note: Participants who have discontinued fenfluramine for reasons of lack of efficacy or intolerability are eligible as prior users.

Approximately 15 participants with DS and 30 participants with LGS will be enrolled in the study.

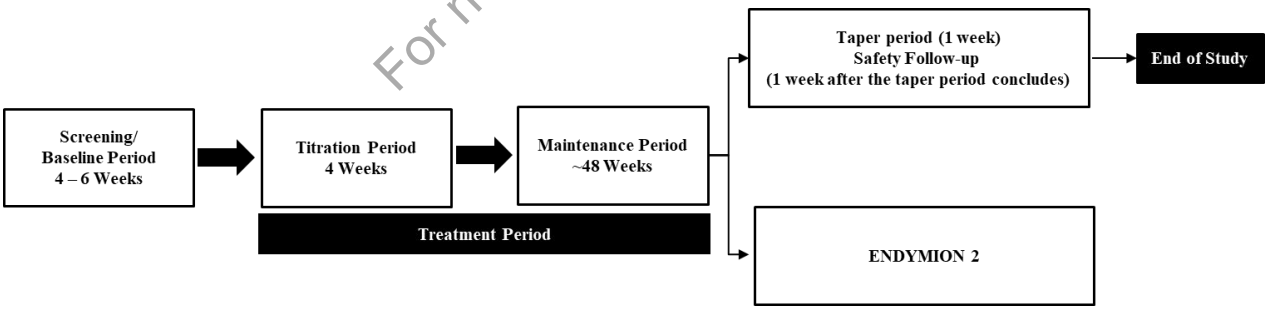
The study will consist of the following periods:

- *A 4- to 6-week screening/baseline period.*
- *Approximately 52-week full treatment period including:*
  - *A 4-week titration period.*
  - *Approximately 48-week maintenance period.*
- *A taper period (up to 1 week) and follow-up period (1 week after the taper period concludes); this will not be required for participants enrolling in the extension study (ENDYMION 2).*
- *Follow-up visit/call occurs approximately 1 week after the taper period concludes.*

This is an open-label study to receive standard-of-care plus soticlestat in participants who have been exposed to fenfluramine. Soticlestat added to current antiseizure therapy will be administered orally BID with or without food (oral or enteral feeds including but not limited to nasogastric tube [NG-tube] or via gastrostomy tube [G-tube] or low-profile gastric tube (Mic-Key Button), or a jejunostomy tube [J-tube]).

A schematic of the study design is shown in Figure 2.a. A schedule of assessments is presented in Section 1.3 of the protocol.

Figure 2.a Schematic of Study Design



The total daily dose of study drug (soticlestat) will be calculated on the basis of body weight at Visit 1 (screening visit) and given BID. The dosing schedules by weight are shown in Table 2.a. *The minimum dose allowed during the study is 100 mg BID (or 100 mg BID equivalent weight-based dosing for weight <45 kg). Participants who cannot tolerate the minimal dose will be discontinued from the study. Participants weighing <45 kg will be dispensed 20 mg mini-tablets. Participants weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets.*

Intermediate doses between dose levels may be allowed after discussing with the medical monitor.

Table 2.a Dosing Schedules by Weight

	Dose 1 (Days 1-7): Adult Reference 100 mg BID		Dose 2 (Days 8-14): Adult Reference 200 mg BID		Dose 3 (Days 15-28): Adult Reference 300 mg BID	
	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini- tablets
10 to <15 kg Weight Reference Dose						
Soticlestat	40 mg BID	2 mini-tablets soticlestat BID	60 mg BID	3 mini-tablets soticlestat BID	100 mg BID	5 mini-tablets soticlestat BID
15 to <30 kg Weight Reference Dose						
Soticlestat	60 mg BID	3 mini-tablets soticlestat BID	120 mg BID	6 mini-tablets soticlestat BID	200 mg BID	10 mini-tablets soticlestat BID
30 to <45 kg Weight Reference Dose						
Soticlestat	80 mg BID	4 mini-tablets soticlestat BID	140 mg BID	7 mini-tablets soticlestat BID	200 mg BID	10 mini-tablets soticlestat BID
≥45 kg Weight Reference Dose						
Soticlestat	100 mg BID	1 tablet soticlestat BID OR 5 mini-tablets soticlestat BID	200 mg BID	2 tablets soticlestat BID OR 10 mini-tablets soticlestat BID	300 mg BID	3 tablets soticlestat BID OR 15 mini-tablets soticlestat BID

BID: twice daily.

Participants <45 kg may request adult size tabs for Dose 3 only.

The dose can be adjusted according to the participant's weight change after completing the initial 12 weeks of the maintenance period, per investigator judgement.

ASMs taken as SOC, should remain stable for initial 12 weeks of the maintenance period, after which, doses can be adjusted based on SOC and investigator judgement.

Rescue medication dose can be adjusted throughout the study as per SOC.

Soticlestat doses should also remain stable for initial 12 weeks of maintenance period, after which it can be adjusted according to participant weight changes and investigator judgement.

The study design allows virtual visits to be conducted via phone or an appropriate platform(s) as long as approved and aligned with institutional or local guidelines. The decision to perform a visit virtually is at the discretion of the investigator.

Screening (Visit 1), Visit 7 and final visit/early termination (ET) must be conducted in clinic or in person (home visits). Safety calls may be conducted virtually.

All other visits can be virtual (visits including assessment of Clinical Global Impression [CGI] scale[s] should be conducted via video, not phone), at investigator discretion and if permitted by local regulations. Additionally, home health visits may be conducted by site staff, if permitted by local regulations. Visit assessment of CGI scale(s) should be conducted via video and not phone.

In addition, any visit identified as virtual in this protocol may be conducted in clinic and in person if requested by the participant/parent or guardian and/or at the investigator's discretion.

Caregivers or principal investigator can request home visits to be conducted by site staff if permissible by local regulations.

2.1.1 Dose Titration Period (4 Weeks)

Participants will take the initial dose of study drug, that is, Dose 1 (100 mg BID adult reference dose, weight-based dosing for weight <45 kg) the morning after the enrollment day (Day -1). Participants receiving the study drug at home through a courier should take it the morning after they receive it.

Approximately 7 days after starting Dose 1, study drug dose will be increased to Dose 2 (200 mg BID adult reference dose, weight-based dosing for weight <45 kg) and continued for approximately 7 days. Seven days after receiving Dose 2, the drug dose can be increased to, Dose 3 (300 mg BID adult reference dose, weight-based dosing for weight <45 kg). If the participants do not experience any tolerability issues, they will continue Dose 3 for the remainder of the titration period.

Participants will only be allowed to increase their dose within the 4-week titration period. A decrease in dose level (to Dose 2 or Dose 1) is allowed during the titration period if required for safety and tolerability. Intermediate doses between scheduled dose levels may be allowed after discussing with the medical monitor.

Participants who cannot tolerate the minimum dose of 100 mg BID (or weight-based equivalent dosing for participants weighing <45 kg) will be discontinued from the study. The maximum allowed dose is 300 mg BID (or weight-based equivalent dosing for participants weighing <45 kg).

The participants/parents or caregivers will be contacted by phone within approximately 2 days following each dose escalation to assess safety and tolerability of the study drug and again at the end of the titration period for that dose. The final dose tolerated by the end of the 4-week titration period should be maintained during the initial 12 weeks of the maintenance period unless tolerability issues arise.

Any changes to the dose levels provided in Table 2.a *may be allowed after further discussion with medical monitor.*

2.1.2 Maintenance Period (Approximately 48 Weeks)

In the absence of safety or tolerability considerations, the final dose level at the end of the titration period should be maintained for the first 12 weeks of the maintenance period. The dose can be adjusted according to the participant's weight change after completing the initial 12 weeks of the maintenance period. During the maintenance period, the dose may be decreased by 1 dose level to the previous lower dose, for safety and tolerability issues. For example, Dose 3 (300 mg BID adult reference dose, weight-based dosing for weight <45 kg) may be reduced to Dose 2 (200 mg BID adult reference dose, weight-based dosing for weight <45 kg), and Dose 2 may be reduced to Dose 1 (100 mg BID adult reference dose, weight-based dosing for weight <45 kg). The minimum dose is Dose 1; participants who cannot tolerate the minimum dose will be discontinued from the

study. The dose may be decreased during the initial 12 weeks maintenance period for safety or tolerability reasons as assessed by the investigator; however, if possible, dose changes should be discussed with the sponsor/designee. After the initial 12 weeks of maintenance period, intermediate doses between dose levels may be allowed after discussion with the medical monitor.

2.1.3 Study Discontinuation/Completion

At the end of overall maintenance period, at Visit 10, participants will have the option to enroll the OLE study ENDYMION 2 on the dose they are receiving in the maintenance period in TAK-935-3004, as deemed appropriate by the investigator.

Participants not entering ENDYMION 2, will begin a 1-week taper period (unless already at the lowest dose). During the taper period, the study drug dose will be tapered down to a lower dose (taper Dose 3 to Dose 2, taper Dose 2 to Dose 1) no more frequently than every 3 days until the study drug is discontinued. On completion of the taper period a safety phone call or visit will be completed approximately 2 weeks after the participant's final visit/ET.

Participants who terminate the study early for reasons other than safety/tolerability may also have the opportunity to join ENDYMION 2 study at sponsor discretion.

2.1.4 Period of Evaluation and Schedule of Study Assessment

Approximately 60 weeks, including up to 6-week screening/baseline period, 52-week treatment period [4-week titration and 48-week maintenance periods], 1-week taper period for those discontinuing study drug, followed by a safety follow-up visit/call 1 week after the taper period ends.

For a schematic of the study design, see Section ***Error! Reference source not found.****. For the Schedule of Activities (SoA), see Section* ***Error! Reference source not found.****.*

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

The primary study objective is descriptive and does not include any formal hypothesis testing. Therefore, there will be no gatekeeping procedure and all the exploratory objectives will be presented regardless of the results of any proceeding objectives.

3.1 Statistical Hypotheses

Not Applicable.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

This study plans to enroll approximately 15 participants with DS and 30 participants with LGS. The study is not powered for hypothesis testing. The sample size is based on an estimation approach to ensure adequate precision to estimate the median change from baseline in convulsive (DS) or MMD (LGS) seizure frequency per 28 days during the first 12 weeks of the maintenance period. With the planned sample sizes, the expected half width of the 95% CI for the median is commensurate with the expected magnitude of the median.

With 15 participants in the DS cohort treated with soticlestat, the expected median percent change from baseline in convulsive seizure frequency during the first 12 weeks of the maintenance period is 35% and expected half width of the 95% CI is 30%.

With 30 participants in the LGS cohort, the expected median percent change from baseline in MMD seizure frequency during the first 12 weeks of the maintenance period is 37% and the expected half width of the 95% CI is 29%.

To determine the expected median and 95% CI half width, simulations were performed assuming the data follow a log normal distribution, and the distribution of the underlying parameters (i.e., mean and SD of the log transform of the data distribution) was developed using results of the phase 2 ELEKTRA study.

5.0 ANALYSIS SETS

5.1 Intent-to-treat (ITT) Analysis Set

All participants who enroll in the study.

5.2 Modified Intent-to-treat (mITT) Analysis Set

All enrolled participants who take at least 1 dose of study drug and are assessed for seizures for at least 1 day in the treatment period.

The mITT analysis set will be used for all efficacy analyses. Subjects who do not enter the maintenance period will not be included in the analyses pertinent to the maintenance period.

5.3 Safety Analysis Set

All participants who take at least 1 dose of study drug.

5.4 Full Analysis Set

Not Applicable.

5.5 Per-Protocol Analysis Set

Not Applicable.

5.6 Pharmacokinetic Analysis Set

There are no PK (pharmacokinetic) data collected. Hence this population is not applicable.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

The analyses are descriptive in nature. No formal hypothesis testing is planned.

Where applicable, variables will be summarized descriptively by cohort (DS and LGS) and by visit.

Categorical variables will be summarized using count (n) and percent (%). Unless otherwise stated, the denominator for percentages is the number of subjects in the group within that analysis set. For any summary statistics by visit, the denominator is the number of subjects that were assessed at that visit. 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 provided.

Mean and median 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. Confidence intervals (CIs) will be presented using the same number of decimal places as the parameter estimate.

Descriptive summaries for primary, exploratory and safety endpoints will be provided by the following groupings (see Table 6.a), unless indicated otherwise.

Table 6.a Grouping Rules for Endpoints

Endpoints	Diagnosis		
	DS	**LGS**	**DS and LGS combined**
Disposition, Demographics and Baseline	DS	LGS	Overall
Efficacy (seizure)	DS **Seizure types:** Convulsive seizures All seizures	LGS **Seizure types:** Major motor drop (MMD) seizures All seizures	Overall (All seizures only)
Exploratory (seizure)	DS	LGS	Overall, (All seizures only)
Exploratory (treatment response)	DS	LGS	-
Exploratory (other than seizure and treatment response)	DS	LGS	-
Medical History, and Prior and Concomitant Medications	DS	LGS	Overall
Safety	DS	LGS	Overall
Extent of exposure	DS	LGS	Overall
Compliance	DS	LGS	Overall

6.1.1 Handling of Treatment Misallocations

The is a single arm study and there is only one allocated treatment. All participants enrolled in the study are included in the ITT Analysis Set. However, for the subject to be included in mITT and Safety Analysis Sets, they need to have taken at least 1 dose of study drug. Further details on mITT and Safety Analysis Sets are presented in sections 5.2 and 5.3.

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 (1-4 weeks; and every 12 weeks from thereafter)
- Other summaries:
– Number of subjects enrolled by country, and site
– Analysis Sets
– Major or significant protocol deviations

If relevant, 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. If relevant, 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.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Patient demographic characteristics will be summarized and listed using the safety analysis set. The variables summarized 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 include:

- Height (cm)
- Weight (kg)
- Body mass index (BMI (kg/m2))

- Number of anti-seizure medications (ASM) taken per subject summarized as 0, 1, 2, 3, etc.
- Convulsive seizure frequency during Baseline Period (DS)
- MMD seizure frequency during Baseline Period (LGS)
- All seizure frequency during Baseline Period (DS, LGS)

6.3.3 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases relevant to the disease under study that resolved before the participant signed the informed consent form. Ongoing conditions are considered concurrent medical conditions.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant laboratory, physical examination, and/or vital signs abnormalities noted at screening examination, according the judgment of the investigator. The condition (i.e., diagnosis) should be described.

Coding of medical history and concurrent medical conditions will be based on the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0 or higher) and will be summarized using System Organ Class (SOC) and MedDRA preferred term. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The summary table will include number and percentages of subjects. SOCs will be sorted using 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.

Summaries of medical history and concurrent medical conditions will be based on the Safety Analysis Set.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

Prior medications are defined as those that were Stopped at or within 90 days before signing the ICF (note: all prior ASMs including fenfluramine use or its reason for discontinuation [if applicable] will be documented regardless of when it was stopped).

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.

Prior medications will be summarized by summarized by Therapeutic Class ATC4 and preferred term. In addition, prior ASMs will be summarized by ATC level 4 and preferred terms.

6.4.2 Concomitant Medications

Concomitant medications/treatments are defined as those given in addition to the study drug:

- *Between the signing of the ICF and participant completion.*
- *Between the first dose of study drug and the end of the follow-up period, inclusive.*
- *Starting before the signing of the ICF and continuing during the study.*

Concomitant 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.

Concomitant medications will be summarized by ATC class level 4, and preferred term. Concomitant ASMs will also be summarized by ATC class level 4, and preferred *term by decreasing frequency of incidence as per* Table 6.a.

Concomitant medications will be listed.

6.5 Efficacy Analysis

All efficacy analysis will be based on the mITT Analysis Set.

6.5.1 Primary Endpoint(s) Analysis

The Primary endpoint is:

- For DS cohort: Percent change from baseline in convulsive seizure frequency per 28 days during the initial 12 weeks of the maintenance period.
- For LGS cohort: Percent change from baseline in major motor drop seizure frequency per 28 days during the initial 12 weeks of the maintenance period.

6.5.1.1 Derivation of Endpoint(s)

For subjects with DS diagnosis percent change from baseline in convulsive seizure frequency per 28 days and total seizure frequency per 28 days will be calculated for the initial 12 weeks of the maintenance period.

For subjects with LGS diagnosis percent change from baseline in MMD seizure frequency per 28 days and total seizure frequency per 28 days will be calculated for the initial 12 weeks of the maintenance period.

Convulsive seizures include the following codes and the descriptions:

- A - Hemiclonic or Focal Clonic
- B - Focal to Bilateral Tonic-Clonic
- C - Generalized Tonic-Clonic
- D - Bilateral Clonic
- E - Convulsive Status Epilepticus

MMD seizures include the following codes and the descriptions:

- A - Hemiclonic or Focal Clonic
- B - Focal to Bilateral Tonic-Clonic
- C - Generalized Tonic-Clonic
- D - Bilateral Clonic
- E - Convulsive Status Epilepticus
- F - Focal with Major Motor Signs (e.g., Hyper motor Seizures or Involving Major Body Areas such as Lower Extremities or Trunk) Leading to Fall or Likely Fall
- G - Tonic Seizures Involving Major Body Areas such as Lower Extremities or Trunk Leading to Fall or Likely Fall
- H - Atonic Seizures Involving Major Body Areas such as Lower Extremities or Trunk Leading to Fall or Likely Fall

Seizure frequency (SF) for each time period and a specified set of seizure types (e.g., convulsive, MMD, all) is calculated using only available (non-missing) data during that period. For example, seizure frequency (SF) per 28 days will be calculated as follows:

$$\text{SF per 28 days} = \frac{\text{Total number of the specific seizure(s) type during the specified period}}{\text{Number of non-missing diary days in the specified period}} \times 28$$

Percent change from baseline in seizure frequency per 28 days during a period will be defined as

$$\frac{(\text{SF per 28 days during period}) - (\text{SF per 28 days during Baseline Period})}{\text{SF per 28 days during Baseline Period}} \times 100$$

Note that the denominator is same for all types of seizures for a specified interval of time for a given subject.

6.5.1.2 Main Analytical Approach

All seizure diary data collected during the Treatment Period will be used even if collected after an intercurrent event. Moreover, for the analysis of primary endpoint, only available diary data from the relevant periods (i.e., non-missing diary days) are used in the calculation of seizure frequency. This approach assumes that the seizure frequency during the missing diary days is equal to the seizure frequency during the non-missing diary days.

Descriptive summaries for percent change in seizure frequencies during the initial 12 weeks of the maintenance period from baseline per 28 days will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Proc univariate with CIPCTLDF option in SAS will be used to obtain the CIs. Descriptive statistics for baseline and maintenance period will also be provided (without CIs).

Results will be presented according to the grouping scheme presented in Table 6.a.

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

6.5.2 Secondary Endpoint(s) Analysis

Not applicable.

6.5.3 Exploratory Endpoints Analysis

6.5.3.1 Percent change from baseline in convulsive (DS) or MMD (LGS) seizure frequency per 28 days during every 12 weeks after the initial 12 weeks of the maintenance period.

The calculation of seizure frequency will be based on approach described in per Section **Error! Reference source not found.**.

For subjects with DS diagnosis, percent change from baseline in frequency per 28 days of convulsive seizure for each 12-week period starting from the date after the initial 12-week maintenance will include:

1. Week 13 to 24 (inclusive) of the maintenance period.
2. Week 25 to 36 (inclusive) of the maintenance period.
3. Week 37-48 (inclusive) of the maintenance period.

For subjects with LGS diagnosis, percent change from baseline in frequency per 28 days of MMD seizure for each 12-week period starting from the date after the initial 12-week maintenance will include:

1. Week 13 to 24 (inclusive) of the maintenance period.

2. Week 25 to 36 (inclusive) of the maintenance period.
3. Week 37-48 (inclusive) of the maintenance period.

Descriptive summaries for percent change in seizure frequencies per 28 days from baseline at for each 12-week period starting from the date after the initial 12-week maintenance will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Proc univariate with CIPCTLDF option in SAS will be used to obtain the CIs. Descriptive statistics for each 12-week period starting from the date after the initial 12-week maintenance will also be provided (without CIs).

In addition, the line graphs plotting percent change from baseline in seizure frequency will be provided, with x-axis as time intervals (every 12 weeks during the maintenance period of the study after the initial 12-week), y-axis as percent change from baseline of seizure frequency.

If a subject has seizure data missing for more than 8 weeks in any 12 weeks of assessment interval after the initial 12 weeks of maintenance, the subject will not be included in the analysis for that interval.

6.5.3.2 Percent change from baseline in convulsive (DS) or MMD (LGS) seizure frequency per 28 days during the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period).

The calculation of seizure frequency will be based on approach described in per Section **Error! Reference source not found.**.

For subjects with DS diagnosis, the endpoint for this analysis will be percent change from baseline in frequency per 28 days of convulsive seizure for the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period).

For subjects with LGS diagnosis, the endpoint for this analysis will be percent change from baseline in frequency per 28 days of MMD seizure for the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period).

Descriptive summaries for percent change from baseline in convulsive (DS) and MMD (LGS) seizure frequency per 28 days during the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period) per 28 days will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Proc univariate with CIPCTLDF option in SAS will be used to obtain the CIs. Descriptive statistics for the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period will also be provided (without CIs).

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.3 Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 12 weeks of the maintenance period.

Percent change from baseline in frequency per 28 days of all seizure types for the initial 12 weeks of maintenance period will be based on approach described in per Section **Error! Reference source not found.**.

Descriptive summaries for percent change from baseline in all seizure types frequency per 28 days during the initial 12 weeks of maintenance period per 28 days will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Proc univariate with CIPCTLDF option in SAS will be used to obtain the CIs. Descriptive statistics for the initial 12 weeks of the maintenance period will also be provided (without CIs).

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.4 Percent change from baseline in total seizure frequency per 28 days of all seizure types every 12 weeks after the initial 12 weeks of the maintenance period.

Percent change from baseline in frequency per 28 days of all seizure types for each 12-week period starting from the date after the initial 12-week maintenance will be calculated based on approach described in per Section **Error! Reference source not found.**. The 12-week periods will include

1. Week 13 to 24 (inclusive) of the maintenance period.
2. Week 25 to 36 (inclusive) of the maintenance period.
3. Week 37-48 (inclusive) of the maintenance period.

Descriptive summaries for percent change in all seizure types frequencies per 28 days from baseline at for each 12-week period starting from the date after the initial 12-week maintenance will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Proc univariate with CIPCTLDF option in SAS will be used to obtain the CIs. Descriptive statistics for each 12-week period starting from the date after the initial 12-week maintenance will also be provided (without CIs).

In addition, the line graphs plotting percent change from baseline in all seizure types frequency will be provided, with x-axis as time intervals (every 12 weeks during the maintenance period of the study after the initial 12-week), y-axis as percent change from baseline of seizure frequency.

If a subject has seizure data missing for more than 8 weeks in any 12 weeks of assessment interval after the initial 12 weeks of maintenance, the subject will not be included in the analysis for that interval.

Results will be presented according to the grouping presented in

Table 6.a.

6.5.3.5 Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period).

Percent change from baseline in frequency per 28 days of all seizure types for the period comprising the 4 weeks of the titration period and first 12 weeks of the maintenance period will be calculated based on approach described in per Section **Error! Reference source not found.**.

Descriptive summaries for percent change from baseline in all seizure types frequency per 28 days during the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period) per 28 days will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Proc univariate with CIPCTLDF option in SAS will be used to obtain the CIs. Descriptive statistics for the initial 16 weeks of the treatment period (4 weeks of titration period + 12 weeks of maintenance period will also be provided (without CIs).

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.6 Percent change from baseline in seizure frequency per 28 days of each seizure type identified at the time of screening or baseline during the maintenance period and full treatment period (52 weeks).

Percent change from baseline in frequency per 28 days of each seizure type during the full Treatment Period (52 weeks) will be calculated using the approach described in Section **Error! Reference source not found.**. For each seizure type, only subjects who experience at least 1 seizure of that type during the screening period (i.e., individuals with a seizure frequency of > 0 at baseline for that type of seizure) will be included in the analysis.

Descriptive summaries for percent change from baseline in for each seizure types (identified at the time of screening or baseline) frequency per 28 days during the full Treatment Period (52 weeks) will include mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median. Proc univariate with CIPCTLDF option in SAS will be used to obtain the CIs. Descriptive statistics for each seizure types (identified at the time of screening or baseline) frequency per 28 days during the full Treatment Period (52 weeks) will also be provided (without CIs).

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.7 Treatment response as defined by ⩾50% reduction in convulsive (DS) or MMD (LGS) seizure frequency per 28 days from baseline every 12 weeks after the initial 12 weeks of the maintenance period.

Subjects with ⩾50% reduction from baseline in convulsive (DS) and MMD (LGS) seizure frequency per 28 days during each of the 12-week maintenance periods will be considered responders for that period.

Descriptive statistics for responder proportions for each period will include count and percentage for proportions for subjects with DS and LGS diagnosis separately. Two-sided 95% CIs will be provided for responder proportions using exact method for each period.

If a subject has seizure data missing for more than 8 weeks in any 12 weeks of assessment interval after the initial 12 weeks of maintenance, the subject will not be included in the analysis for that interval.

6.5.3.8 Treatment response as defined by ⩾50% reduction in convulsive (DS) or MMD (LGS) seizure frequency per 28 days from baseline during the initial 16 weeks of the full treatment period (4 weeks of titration period + 12 weeks of maintenance period).

Subjects with ⩾50% reduction from baseline in convulsive (DS) and MMD (LGS) seizure frequency per 28 days during the initial 16 weeks of the full treatment period will be considered responders for that period.

Descriptive statistics for responder proportions for each period will include count and percentage for proportions for subjects with DS and LGS diagnosis separately. Two-sided 95% CIs will be provided for responder proportions using exact method.

In addition, the responder proportion will be summarized for the initial 12 weeks of the maintenance period.

6.5.3.9 Clinical Global Impression of Improvement (CGI-I) (clinician).

The CGI-I (clinician) is a 7-point Likert scale that the investigator uses to rate a participant's change (improvement) in overall seizure control, nonseizure symptoms, and behavior, as well as how well the participant is tolerating study drug and side effects, compared with baseline (before treatment with the study drug). The participant will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The investigator or designee will complete the CGI-I at Visit V6, V7, and V10. The baseline visit for this assessment occurs at visit V2. *For assessing baseline disease severity to inform subsequent CGI-I, the investigator or designee will complete the CGI Baseline questionnaire. The investigator or designee will record their overall clinical impression of disease severity at baseline. They will interview the participant (if appropriate) or parent/caregiver and use input from the participant or parent/caregiver to inform their overall clinical impression assessment (Guy 1976).*

For each visit, count and percentage for proportions for each of the 7-point Likert scale categories will be presented. Responses will be dichotomized as improvement (scores 1, 2, and 3) or "no improvement or worse" (scores 4, 5, 6, and 7) and the count and percentage of these two categories will be provided by visit. Two-sided 95% CIs will be provided for percentage of improvement using exact method at each visit.

The baseline questionnaire data will not be used in the analyses.

6.5.3.10 Caregiver Global Impression of Improvement (Care GI-I).

The Care GI-I is a 7-point Likert scale that the caregiver uses to rate improvement in overall seizure control, behavior, safety and tolerability after the initiation of study drug relative to baseline (before treatment with the study drug). The participant will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The parent/caregiver will complete the Care GI-I via interview at Visit V6, V7, and V10. The baseline visit for this assessment occurs at visit V2.

For assessing Care GI Baseline of overall illness severity, investigator or designee will record on behalf of the participant (if appropriate) or parent/caregiver's assessment of the participant's overall condition using the same questionnaire.

The analysis and data summaries will follow the same approach as for the CGI-I (clinician) analysis, per Section 6.5.3.9.

Results will be presented according to the grouping presented in Table 6.a

Table 6.a.

6.5.3.11 CGI-I Seizure Intensity and Duration.

The CGI-I Seizure Intensity and Duration instrument is used by the investigator (with input from the parent/caregiver as needed) to rate changes in intensity and/or duration of the most impactful seizures compared with the baseline assessment. The participant's symptoms will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The investigator or designee will complete the CGI-I Seizure Intensity and Duration in consultation with the primary caregiver at Visits V6, V7, and V10. The baseline visit for this assessment occurs on visit V2.

The analysis and data summaries will follow the same approach as for the CGI-I (clinician) analysis, per Section 6.5.3.9.

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.12 CGI-I Nonseizure Symptoms completed by clinician with input from the caregivers.

The CGI-I Nonseizure Symptoms instrument is a series of single-item assessments that the investigator (with input from the parent/caregiver as needed) uses to rate improvement in the symptoms and impacts in select nonseizure domains (including communication, alertness, and disruptive behaviors) since initiating the study drug at baseline. The participant will be rated by the investigator as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse).

The investigator or designee will complete the CGI-I Nonseizure Symptoms instrument in consultation with the primary caregiver at Visits V6, V7, and V10. The baseline visit for this assessment occurs on visit V2.

The analysis and data summaries will follow the same approach as for the CGI-I (clinician) analysis, per Section 6.5.3.9.

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.13 Quality of Life Inventory-Disability (QI-Disability).

The QI-Disability tool is a parent/caregiver-reported questionnaire that evaluates quality of life in children with intellectual disabilities. It contains 32 items covering 6 domains of quality of life: physical health (4 items), positive emotions (4 items), negative emotions (7 items), social interaction (7 items), leisure and the outdoors (5 items), and independence (5 items).

Items are rated on a Likert scale of: Never = 0, Rarely=25, Sometimes=50, Often=75 and Very Often=100; the Negative Emotions domain items are reverse coded (i.e., Never=100, Rarely=75, Sometimes=50, Often=25 and Very Often=0). The domain score is the sum of the non-missing items in the domain divided by the number of non-missing items, and the total score for the QI-Disability questionnaire is the sum of the domain scores divided by 6. The domain score is

considered non-missing provided at least one item received a score. The total score is considered non missing if all domain scores are non-missing.

The parent/caregiver-reported questionnaires will be administered at Visits V2 (baseline), V7, and V10.

The change from baseline (in total score) will be summarized descriptively by visits as a continuous variable. Mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median will be provided at each visit.

The line graph plotting median and 95% CI for the percent change from baseline QI-Disability score will be provided, with x-axis as time.

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.14 Change in EQ-5D 5-level version (EQ-5D-5L) and EQ-5D visual analogue scale (EQ VAS) scores.

The EQ-5D-5L is the 5–response level version of the EQ-5D instrument. The EQ-5D-5L is a preference-based measure of health status suitable for calculating quality-adjusted life years to inform economic evaluations. It consists of 2 sections, a descriptive system questionnaire and the EQ VAS. The questionnaire provides a descriptive profile across the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the EQ-5D-5L version, each dimension has 5 response levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The parents or caregivers are asked to indicate their own health quality of life by selecting the most appropriate statement in each of the dimensions. In addition, the EQ VAS is used to indicate the general health status by rating their health "today" from 0 (worst) to 100 (best health you can imagine). These questionnaires will be administered at Visits V2 (baseline), V7, and V10.

EQ-5D-5L responses are coded as: 1=no problems; 2=slight problems; 3=moderate problems; 4=severe problems; 5=unable to/extreme problems. EQ-5D-5L will be summarized descriptively by visit including baseline by presenting the count and percentage of responses in each level within each dimension. In addition, a dichotomization based on 'no problems' (level = 1) vs. 'any problems' (levels = 2, 3, 4, and 5) will be summarized using a shift table over time. A shift table will be provided by comparing the results (dichotomous category) at each scheduled post-baseline visit with those at the baseline visit. The count and percentages in each category based on dichotomization will be provided over time.

EQ-VAS scores will be summarized descriptive by visit. Change in EQ-VAS from baseline will be summarized descriptively as a continuous variable. Mean, SD, median, Q1, Q3, minimum, maximum, and distribution-free 95% CI for the median will be provided at each visit.

The line graph plotting median and 95% CI for the percent change from baseline EQ-VAS score will be provided, with x-axis as time.

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.15 Caregiver satisfaction questionnaire.

The caregiver satisfaction questionnaire is a 7-point Likert scale that the caregiver uses to rate overall satisfaction with soticlestat. The parent/caregiver is asked to consider the study participant's symptoms over the past 4 weeks and rate overall satisfaction with soticlestat using the following rating options: extremely satisfied, very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied, extremely dissatisfied.

The parent/caregiver will complete the caregiver satisfaction questionnaire at Visit V7.

Response will be summarized descriptively by presenting count and percentage of responses in each level. In addition, a dichotomization based on satisfied (extremely satisfied, very satisfied, satisfied) vs not satisfied (neither satisfied nor dissatisfied, dissatisfied, very dissatisfied, extremely dissatisfied) will be summarized using count and percentage. Two-sided 95% CIs will be provided for proportion satisfied using exact method.

Results will be presented according to the grouping presented in Table 6.a.

6.5.3.16 Days when rescue ASM is used.

Use of rescue anti-seizure medications (ASM) is to be recorded in the CRF in the Concomitant Medications (Rescue Anti-Seizure) folder along with start and end date of medication. Based on the start and end dates for all rescue ASMs taken by a subject, the number of days during the study when rescue ASM is used will be derived. The proportion of days during the study period will also be calculated, using the number of days during the study between date of first dose (included) and date of the End of Maintenance (or Early Termination) visit as the denominator (included). The number of days when rescue ASM is used will be summarized descriptively.

For this analysis, missing dates will be imputed in the most conservative manner. The missing start dates for rescue ASM will be imputed to the first day of the month or the first day of the study (whichever is later) if day is missing but month and year are known, and to the first day of the year or the first day of the study (whichever is later) if day and month are missing but year is known. If year is missing, the rescue ASM will conservatively be assumed to have started on the first day of the study. Missing end dates for rescue ASM will be imputed to the last day of the month or the last day of the study (whichever is earlier) if day is missing but month and year are known, and to the last day of the year or the last day of the study (whichever is earlier) if day and month are missing but year is known. If year is missing, the rescue ASM will conservatively be assumed to have ended on the last day of the study.

Results will be presented according to the grouping presented in Table 6.a.

6.5.4 Subgroup Analyses (if applicable)

Not applicable.

6.6 Safety Analysis

Safety analyses will be performed using the safety analysis set. Results will be presented descriptively. AEs will be coded using the Medical Dictionary for Regulatory Activities

(MedDRA). TEAEs will be summarized using Preferred Terms and primary System Organ Classes.

Data summaries will be displayed for incidence of TEAEs, clinical laboratory variables, and vital sign parameters. Descriptive statistics such as mean, median, SD, Q1, Q3, minimum, maximum etc. will be provided, as appropriate. For change from baseline and percent change from baseline, median and distribution-free two sided 95% CIs will be provided, as appropriate. For AEs, counts and percentages will be presented by SOC and PT.

Ophthalmological evaluations and C-SSRS will be listed by participant.

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:

- A Treatment-emergent adverse event (TEAE) is defined as any AE that starts or increases in severity on or after the first dose of the study drug of OLE. Events where the onset date is the same as the study drug start date are assumed to be treatment emergent, unless the investigator indicates on the CRF that the event occurred before the first dose.
- Treatment-emergent SAE: A TEAE that is serious.

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 double-blind study medication (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 the 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 the study medication and the stop date is not prior to the date of the 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 the 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.a. The summary tables will include the count and percentage [n (%)] of subjects. The tables will include number of events, as appropriate. 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 Adverse Events of Special Interest

The following AEs of special interest will be summarized. Please refer to the protocol for details.

- *Potential drug-drug interaction between soticlestat and perampanel leading to increased seizure frequency*
- *Cataracts*
- *Psychosis*

AESIs must be recorded as AEs in the eCRF within 24 hours. An evaluation form along with all documentation must be submitted to the sponsor.

The number and percentage of AEs of special interest and number of events will be presented by groups similar to TEAEs. Adverse events of special interests will be categorized and presented by SOC and PT in the same manner that described in Section **Error! Reference source not found.** and per the grouping presented in Table 6.a.

6.6.3 Other Safety Analysis (if applicable)

6.6.3.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and behavior will be assessed in participants aged ≥6 years by use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, participant endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency), and suicidal behavior (actually, interrupted, and aborted attempts at suicide).

C-SSRS will be listed by participant.

6.6.3.2 Ophthalmological evaluations.

An ophthalmologic evaluation will be conducted by a pediatric ophthalmologist or neuroophthalmologist preferably, although an adult ophthalmologist or an optometrist experienced with examining children may be allowed after discussion with the medical monitor. The ophthalmologic evaluation may include:

1. *Age and developmentally appropriate quantitative visual acuity.*

If the participant is unable to perform quantitative visual acuity assessment due to age or developmental ability, a qualitative assessment should be attempted.

2. *Bilateral red reflex test (also known as Bruckner transillumination test), to assess for lens abnormalities.*

These evaluations are to be conducted at baseline (V1) *(between the screening and enrollment visits), at Day 112 (±2 weeks)* (V7) *and at Day 364 (±1 weeks)* (V10) *or at the ET visit for those participants who do not complete the study.*

Additional unscheduled ophthalmological assessments may be conducted during the course of this study, if recommended by the ophthalmologist.

The parameters, visual acuity, cataract screening and fundoscopic examination in ophthalmological evaluations for each group (as per Table 6.a) will be summarized for baseline, and each post-baseline visit.

The number and percentages of subjects having significantly declined visual acuity will be provided over time. Similarly, subjects having anterior or posterior lens opacities in cataract screening and subjects having optic nerve exam as abnormal in fundoscopic examination will be summarized.

All ophthalmological evaluation data will be listed.

6.6.4 Extent of Exposure and Compliance

Extent of exposure (in weeks) 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 weeks) will be summarized (descriptive statistics such as N, mean, SD, median, minimum, and maximum) for all patients by group specified in Table 6.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 will be provided by dose level (1. 2. 3) at each visit.

The primary method of assessing compliance will be based on the number of returned tablets.

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

1) Using the electronic 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 is supposed to take.

For each treatment 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 will be presented. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum). In addition, Number, and percentage of subjects with seizure diary compliance will be summarized by <80% and >=80%. The drug compliance will be based on the safety analysis set.

Seizure diary compliance is assessed over the period starting from date of first dose and ending on the date of the follow-up visit. Seizure diary compliance will be summarized in a similar fashion. Compliance is calculated as:

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

The **Baseline Period** for the purpose of percent change from baseline analysis of seizure frequencies includes the first day of screening (V1) and all days up to and including the day before first dose of study drug.

Seizure diary compliance will be based on the mITT analysis set.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Not applicable.

6.7.2 Pharmacodynamic Analysis

Not applicable.

6.7.3 Biomarker Analysis

Not applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.9 Other Analyses

Not applicable.

6.10 Interim Analyses

Interim data cuts from this ongoing study will be analyzed to support any regulatory submissions. Since there is no hypothesis testing involved, any interim analysis performed will not require any type-I error adjustment.

6.11 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

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

9.2.1 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing assessment prior to the first dose of the study drug. In the case where the last non-missing measurement (except AE and concomitant medications) and the first dose coincide at the same time, or the same date if time of the measurement is not collected, that measurement will be considered as baseline value. For seizure frequency, the prospective 4 to 6- week baseline period of the study will be used to compute the baseline frequency.

9.2.2 Definition of Visit Windows

Unless otherwise specified, all the summary tables by visit will use the values (post-baseline) selected from analysis visit windows. A windowing convention using the midpoint technique (based on study days for each assessment as specified in the protocol schedule of assessments) will be used to determine the mapping of a datapoint to an analysis visit window. When more than one record falls into one analysis visit window, the rules specified below will be applied to select the appropriate record for summary tables. Note that, if multiple measurements are recorded at the same day and time, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) can be used.

Safety (Lab, Vitals, ECG etc.):

- When more than one record for a parameter is obtained in an analysis visit window, the latest one will be used for summary.

Other (Care GI-I, CGI-I, etc.):

- If multiple assessments occur in the same window, the assessment done at the scheduled visit will be summarized at 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 protocol schedule of assessments) will be used for summary.
- If there are two unscheduled assessments within the window and they are equally close to the scheduled visit, the later assessment will be used for summary.

Listings will include all assessments.

9.3 Analysis Software

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

Signature Page for Statistical_Analysis_Plan_TAK-935-3004
Title: SAP

Approval	[redacted] Statistics 29-Jun-2023 06:17:17 GMT+0000

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