Statistical Analysis Plan

NCT Number: NCT05163314

Title: A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies To Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects With Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2)

Study Number: TAK-935-3003

Document Version and Date: Amendment 1, 21 May 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-935-3003

Study Title:

A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies to Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects with Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2)

Phase: Phase 3

Version: Amendment 1

Date: 21-May-2024

Prepared by: [redacted], Ph.D.

Based on:

Protocol Version: Amendment 2

Protocol Date: 28 February 2023

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	25-FEB-2022	[Not Applicable]
Amendment 1	21-May-2024	Added two endpoint and analysis for 1) Assess acceptability and palatability questionnaires 2) [redacted] Updated wordings including revised endpoints per Protocol Amendment 2. Added seizure frequency calculation from uncountable seizure cluster. Added Clarification on analyses of PK and plasma 24 HC level with efficacy response. Removed Adverse Events (AEs) for special interest summary based on Retrospective AE by PT terms. Updated the definition of categories based on Columbia-Suicide Severity Rating Scale (C-SSRS) for analyzing shift tables. Updated analyses section for Ophthalmological evaluations, ECG interpretations and selection of laboratory in different analyses. Added additional exploratory analyses to explore growth trends in height and weight for 18 years old or younger subjects. Added clarification on selecting records from multiple records from an analysis visit window.

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ABBREVIATIONS

24HC	24*S*-hydroxycholesterol
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
ASM	Antiseizure medication
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
Care GI-I	Caregiver Global Impression of Improvement
CGI-I	Clinical Global Impression of Improvement
CI	confidence interval
CH24H	cholesterol 24S-hydroxylase
COVID-19	coronavirus disease 2019
CRF	Case Report Form
CYP	cytochrome P450
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
[redacted]	[redacted]
[redacted]	[redacted]
G-tube	gastrostomy tube
GCP	Good Clinical Practice
IB	investigator's brochure
ICF	informed consent form
IGF-1	insulin-like growth factor 1
ITT	intention-to-treat
IDMC	independent Data Monitoring Committee
J-tube	jejunostomy tube
LGS	Lennox-Gastaut Sydnrome
LLOQ	Lower limit of quantitation

LOCF	last observation carried forward
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMD	major motor drop
OLE	open-label extension
PEG tube	percutaneous endoscopic gastrostomy tube
PEQ	patient experience questionnaire
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient reported outcome
PT	Preferred Term (MedDRA)
OLE	open-label extension
Q1	25th percentile
Q3	75th percentile
QI-Disability	Quality of Life Inventory-Disability
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
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

The primary objective of this study is to assess the long-term safety and tolerability of soticlestat when administered as adjunctive therapy to (SOC) (eg, ASMs, vagus nerve stimulation, ketogenicdiet, modified Atkins diet) in subjects with DS or LGS.

1.1.2 Secondary Objective(s)

The secondary objectives, in subjects with DS or LGS receiving soticlestat as adjunctive therapy to SOC, are the following:

- *To assess the effect of soticlestat on seizure frequency (convulsive seizures for the DS cohort, MMD seizures for the LGS cohort, and total seizure count for each cohort).*
- *To assess the effect of soticlestat on the Clinical Global Impression of Improvement (CGI-I)(clinician) and Caregiver Global Impression of Improvement (Care GI-I).*
- *To assess the effect of soticlestat on CGI-I Seizure Intensity and Duration.*
- *To assess the effect of soticlestat on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregiver.*
- *To assess the effect on Quality of Life Inventory-Disability (QI-Disability).*

1.1.3 Additional Objective(s)

1.1.3.1 Exploratory Objective

The exploratory objectives, in subjects receiving soticlestat as adjunctive therapy SOC are the following:

- [redacted]
- *Days when rescue ASMs are used.*
- [redacted]
- *Correlation of soticlestat exposure (PK) or effect on plasma 24HC (pharmacodynamics) with efficacy.*
- *Characterization of subject and caregiver study experience (selected sites only).*
- *Assess the palatability and acceptability of the soticlestat tablets and mini-tablets taken orally, either intact or crushed and mixed with applesauce, yogurt, or other liquid of similar consistency, in children with DS or LGS.*
- [redacted].

1.2 Endpoints

1.2.1 Primary Endpoints (Safety)

The primary endpoints (safety) include the following:

- *Incidence of TEAEs.*
- *Incidence of abnormal values for clinical laboratory tests and electrocardiogram (ECG) evaluations.*
- *Change from baseline in clinical laboratory tests values, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) and ECG parameters.*
- *Change from baseline in height and weight for all age groups.*
- *Absolute value for Tanner stage for children 6 to 17 years of age during the study.*
- *Absolute values for IGF-1 for children 2 to 17 years of age during the study.*

1.2.2 Secondary Endpoint(s)

The secondary endpoints include the following:

- *Percent change from baseline in total seizure frequency per 28 days for each (DS and LGS) cohort.*
- *Percent change from baseline in convulsive seizure frequency (DS) per 28 days.*
- *Percent change from baseline in MMD seizure frequency (LGS) per 28 days.*
- *Effect on the CGI-I and Care GI-I.*
- *Effect on CGI-I Seizure Intensity and Duration.*
- *Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregivers.*
- *Effect on QI-Disability.*

1.2.3 Exploratory Endpoints

The exploratory endpoints include the following:

- [redacted]
- *Days when rescue ASM is used.*
- [redacted]
- [redacted]
- *Percent change from baseline in plasma 24HC.*

- *Plasma concentrations of soticlestat and its metabolite(s) at multiple time points.*
- *Soticlestat exposure (PK)–plasma 24HC level (pharmacodynamics) analysis and relationship of PK or pharmacodynamics to efficacy response.*
- *Qualitative caregiver inputs about the caregiver's and subject's experience (selected sites only).*
- *Acceptability and palatability questionnaires*
- [redacted]

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a multisite, phase 3, OLE study designed to obtain additional safety and tolerability data related to soticlestat administered long-term in subjects who participated in either of the antecedent phase 3 clinical studies, TAK-935-3001 (subjects with DS) or TAK-935-3002 (subjects with LGS). Additional aims are to assess efficacy in terms of seizure frequency, by the investigator (by CGI-I) as well as by the caregivers (by Care GI-I, CGI-I in non–seizure-related symptoms, impact on quality of life, PK, and PD (24HC) of soticlestat administration in pediatric and adult subjects with DS or LGS.

Subjects will be eligible to enroll in this study if they have received at least 12 weeks of treatment (combined titration and Maintenance Period) with the study drug in the antecedent study and do not have a serious or severe AE that, in the investigator's or sponsor's opinion, was related to the study drug and would make it unsafe for the patient to continue receiving the study drug.

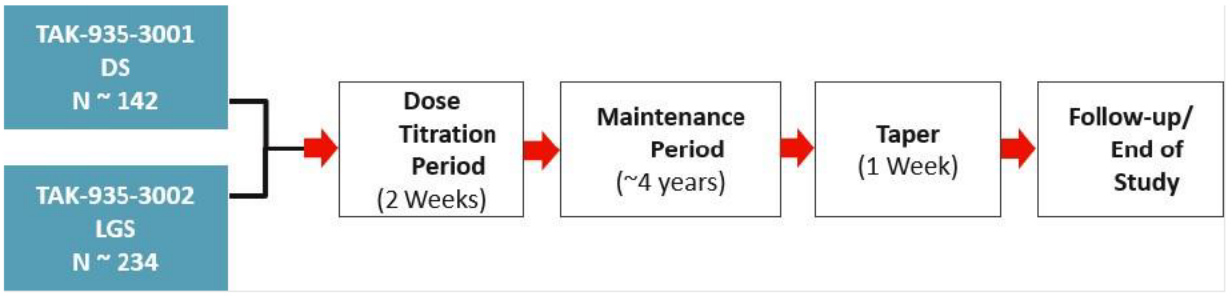
Approximately 400 male and female pediatric and adult subjects from the 2 antecedent phase 3 studies will be rolled over into this study. Most of the assessments from the prospective baseline of the antecedent study will be used as baseline for this study. Treatment received during the antecedent study will remain blinded.

After an initial 2-week titration period, the planned treatment duration is approximately 4 years, or until the study is stopped at the discretion of the sponsor, or the product is approved for marketing. Subjects who complete the full maintenance period or discontinue early will undergo an approximately 1-week taper period (if on dose level 2 or 3), followed approximately 2 weeks later by a safety follow-up visit or phone call.

Soticlestat added to current antiseizure therapy will be administered orally BID 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 medical monitor or sponsor. Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.

A schedule of assessments is listed in Appendix A of the protocol. *A schematic of the study design is shown in* Figure 2.a.

Figure 2.a Schematic of Study Design



DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome

The total daily dose of soticlestat will be calculated based on body weight at Visit 1 and given twice a day (BID). *Subjects will receive Dose 2, the initial dose of study drug (200 mg BID adult reference dose, weight-based dosing for weight <45 kg) for the first 7 days, then study drug dose will be increased to the target dose, Dose 3 (300 mg BID adult reference dose, weight-based dosing for weight <45 kg). If the subjects do not experience any tolerability issues, they will remain on Dose 3 for the remaining 7 days of the titration period, safety follow-up phone calls will again be made after the first dose on the new amount and at the end of the 7-day titration period.*

The dosing schedules by weight are shown in Table 2.a through Table 2.d. The minimum dose allowed during the study is 100 mg BID (weight-based dosing <45 kg). Subjects who cannot tolerate the minimum dose will be discontinued from the study. Subjects weighing <45 kg will be dispensed 20 mg mini-tablets for the titration period followed by 20 mg mini-tablets or 100 mg tablets for the maintenance period. Subjects weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets. The dose may be adjusted every 6 months, depending on the subject's weight.

Table 2.a Dosing Schedules by Weight, 10 to <15 kg

10 to <15 kg Weight Reference Dose					
Dose 1, Minimum Dose(as needed): Adult Reference 100 mg BID		**Dose 2, Starting Dose(Days 1-7): Adult Reference 200 mg BID**		**Dose 3, Target Dose (Days 8-14, and continuing): Adult Reference 300 mg BID**	
Soticlestat (mg/dose)	**No. Tablets/ Mini-tablets**	**Soticlestat (mg/dose)**	**No. Tablets/ Mini-tablets**	**Soticlestat (mg/dose)**	**No. Tablets/ Mini-tablets**
40 mg BID	2 mini tabs BID	60 mg BID	3 mini tabs BID	100 mg BID	1 tab BIDOR 5 mini tabs BID

BID: twice daily; No.: number.

Table 2.b Dosing Schedules by Weight, 15 to <30 kg

15 to <30 kg Weight Reference Dose					
Dose 1, Minimum Dose (as needed): Adult Reference 100 mg BID		Dose 2, Starting Dose (Days 1-7): Adult Reference 200 mg BID		Dose 3, Target Dose (Days 8-14, and continuing): Adult Reference 300 mg BID	
Soticlestat (mg/dose)	No. Tablets/ Mini-tablets	Soticlestat (mg/dose)	No. Tablets/ Mini-tablets	Soticlestat (mg/dose)	No. Tablets/ Mini- tablets
60 mg BID	3 mini tabs BID	120 mg BID	6 mini tabs BID	200 mg BID	2 tabs BID OR 10 mini tabs BID

BID: twice daily; No.: number.

Table 2.c Dosing Schedules by Weight, 30 to <45 kg

30 to <45 kg Weight Reference Dose					
Dose 1, Minimum Dose (as needed): Adult Reference 100 mg BID		Dose 2, Starting Dose (Days 1-7): Adult Reference 200 mg BID		Dose 3, Target Dose (Days 8-14, and continuing): Adult Reference 300 mg BID	
Soticlestat (mg/dose)	No. Tablets/ Mini-tablets	Soticlestat (mg/dose)	No. Tablets/ Mini-tablets	Soticlestat (mg/dose)	No. Tablets/ Mini- tablets
80 mg BID	4 mini tabs BID	140 mg BID	7 mini tabs BID	200 mg BID	2 tabs BID OR 10 mini tabs BID

BID: twice daily; No.: number.

Table 2.d Dosing Schedules by Weight, ≥45 kg

≥45 kg Weight Reference Dose					
Dose 1, Minimum Dose (as needed): Adult Reference 100 mg BID		Dose 2, Starting Dose (Days 1-7): Adult Reference 200 mg BID		Dose 3, Target Dose (Days 8-14, and continuing): Adult Reference 300 mg BID	
Soticlestat (mg/dose)	No. Tablets/ Mini-tablets	Soticlestat (mg/dose)	No. Tablets/ Mini-tablets	Soticlestat (mg/dose)	No. Tablets/ Mini- tablets
100 mg BID	1 tab BID OR 5 mini tabs BID	200 mg BID	2 tabs BID OR 10 mini tabs BID	300 mg BID	3 tabs BID OR 15 mini tabs BID

BID: twice daily; No.: number.

2.1 Dose Titration Period (2 Weeks)

*Subjects will receive soticlestat Dose 2 for their weight (*Table 2.a *through* Table 2.d*) for the first7 days after Visit 1. A safety follow-up call will be made after the first dose. Study drug dose will then be increased to Dose 3 for 7 days, followed by a safety follow-up phone call. A decrease in dose level (to Dose 2 or Dose 1) is allowed if required for safety and tolerability. Subjects who cannot tolerate the minimum dose of 100 mg BID (or weight-based equivalent dosing <45 kg) will be discontinued from treatment. The maximum allowed dose is 300 mg BID. The subjects/parents or caregivers will be contacted by phone within the first 2 days following dose escalation to assess safety and tolerability of the study drug. The final dose tolerated by the end of the 2-week titration period should be maintained until the end of the maintenance period, unless tolerability issues arise.*

2.2 Maintenance Period (4 Years)

In the absence of weight change or safety or tolerability considerations, the final dose tolerated by the end of the 2-week titration period should be maintained until the end of the maintenance period. However, 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 may be reduced to Dose 2, and Dose 2 may be reduced to Dose 1. The minimum dose is Dose 1 (100 mg BID adult reference dose; or weight-based equivalent dosing for <45 kg); subjects who cannot tolerate the minimum dose (Dose 1) will be discontinued from treatment. Doses between the scheduled dose levels may be allowed once for safety and tolerability (as assessed by the investigator). The dose may be adjusted every 6 months, depending on the subject's weight.

2.3 Study Discontinuation/Completion

At the end of the maintenance period, whether after the full duration or for early termination, the dose will be tapered for approximately 1 week (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) every 3 days until the study drug is discontinued. After tapering, the subject/caregiver will complete a safety follow-up phone call (or visit) approximately 2 weeks after the last dose of study drug and exit from the study.

Subjects who discontinue study drug treatment before the completion of the study will continue to be followed per protocol and at minimum maintain daily seizure diary until the final follow up phone call.

2.4 Overall Schedule of Study Assessments

The schedule of assessments is presented by visit in Appendix A of the protocol and study assessment methods are presented in Section 9 of the protocol. The baseline visit (Visit 1) can occur on the same day as the end-of-treatment visit of the antecedent study. If these 2 visits are on different days, collection of concomitant medication, serum pregnancy test, C-SSRS, and ECG should be repeated on Visit 1. Other identical safety assessments (weight, height, vital signs, physical examination, neurological examination, ophthalmological examination, hematology and serum chemistry, urinalysis) and quality of life assessments taken at the subject's last visit of the

antecedent study do not need to be repeated if performed within 21 days before Visit 1 but could be performed at the discretion of the investigator. After Visit 1, subsequent visits will occur at Week 1 (Day 7), 4, 13, 26, 39, 52 (all in Year 1); every 13 weeks starting with Week 65 in Year 2; every 26 weeks starting with Week 130 in Year 3.

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. Blood samples will be collected for soticlestat PK and 24HC analysis.

Table 2.e Antecedent TAK-935 Phase 3 studies included for this OLE study

Study	Brief Summary of Design	Population	Seizure Types	Comments
SKYLINE TAK-935-3001	A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of soticlestat as adjunctive therapy in pediatric and young adult subjects with Dravet Syndrome (DS). It has 4 weeks of dose titration period and 12 weeks of maintenance period. Treatment arms: weight based soticlestat or placebo (up to 300 mg BID).	Approximately 142 male and female pediatric and young adult subjects with DS will be randomized.	Convulsive seizure, All-seizure.	Actual number of subjects Randomized was 144.
SKYWAY TAK-935-3002	A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of soticlestat as adjunctive therapy in pediatric and young adult subjects with Lennox-Gastaut Syndrome (LGS). It has 4 weeks of dose titration period and 12 weeks of maintenance period. Treatment arms: weight based soticlestat or placebo (up to 300 mg BID).	Approximately 234 male and female pediatric and adult subjects with LGS will be randomized.	Major motor drop (MMD) seizure, All-seizure	Actual number of subjects randomized was 270.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable. There will be 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

The sample size is determined by the number of subjects who roll over from the double-blind antecedent studies (approximately 400 subjects based on the expected enrollment of those studies). No formal sample size calculation is performed.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

All treated subjects (subjects who take at least 1 dose of study drug) will be included in the safety analysis set.

5.2 Intent-to-Treat Analysis Set

All enrolled subjects will be included in the intent-to-treat (ITT) 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 ITT (mITT) analysis set.

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

5.4 Pharmacokinetic Analysis Set

All subjects in the safety analysis set who have at least one measurable soticlestat or metabolite plasma concentration will be included in the PK analysis set.

5.5 PD Analysis Set

All subjects in the safety analysis set who have at least one measurable plasma 24HC concentration will be included in the PD analysis set.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Where applicable, 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. Generally, "Missing" will be displayed as a category to represent missing data, if necessary. If missing is not a category or not presented, 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, standard deviation (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. Confidence intervals (CIs) will be presented using the same number of decimal places as the parameter estimate.

For the definition of baseline, unless otherwise specified, please refer to Section 9.2.2.

Unless otherwise specified, please refer to Section 9.2.3 for the definition of visit windows for the specified endpoints. Unless otherwise specified, please refer to Section 9.2.4 for the rules of selecting appropriate record from multiple assessments mapped into an analysis visit window for the specified endpoints.

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

Table 6.a Grouping Rules for Endpoints

Endpoints	**Antecedent Studies**		
	TAK-935-3001 (SKYLINE)	**TAK-935-3002 (SKYWAY)**	**All Studies**
Disposition, Demographics and Baseline	DS (Placebo, TAK-935, All)	LGS (Placebo, TAK-935, All)	Overall
Efficacy (seizure only)	DS **Seizure types:** Convulsive seizures All seizures	LGS **Seizure** types: Major motor drop (MMD) seizures All seizures	Overall (All seizures only)
Efficacy (other than seizure)	DS	LGS	Overall, as appropriate
Medical History, and Conmeds	DS	LGS	Overall
Safety (AE, labs, ECG, Vitals, and Ophthalmogical Examination)	DS	LGS	Overall
PK	DS	LGS	Overall

PD	DS	LGS	Overall
Acceptability & Palatability, [redacted]	DS	LGS	Overall
Extent of exposure	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; etc. and every 26 weeks from thereafter)
- Other summaries:

– Number of subjects enrolled by country, and site

– Analysis Sets

– Major or 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.).

Significant protocol deviations will be summarized by site and overall based on the ITT analysis set. 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.

A summary table for all analysis sets will be created. 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 will be summarized and listed using the safety analysis set.

Demographic variables 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/m^2))
- Number of anti-seizure medications (ASM) taken per subject categorized 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 and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0 or higher) 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 table 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.

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

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 and Anti-seizure medications (ASMs) will be flagged.

Prior medications will be summarized by summarized by ATC class level 2, ATC class level 4, and preferred term. In addition, prior ASMs will be summarized by ATC level 4 and preferred terms. The highest available ATC level will be reported if ATC 4 level is not available.

6.4.2 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. A by-subject listing of concomitant medications will include all medications (including vaccinations) taken during the study regardless of the timing for the start of the medication. All medications stopped before *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 the study as well as the number and percentage of subjects who took each type of medication will be presented as per Table 6.a*. Medications will be presented according to their WHO Drug Dictionary Anatomic Therapeutic Chemical (ATC) class level 4 and preferred drug name within ATC class level 4 by decreasing frequency of incidence as per* Table 6.a*.*

Concomitant medications will be summarized by ATC class level 2, ATC class level 4, and preferred term as per Table 6.a. Concomitant ASMs and concomitant anti-seizure rescue medications will also be summarized by ATC class level 4, and preferred term. The highest available ATC level will be reported if ATC 4 level is not available.

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

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 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 two-sided 95% 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 Seizure Endpoint(s) Analysis:

The seizure endpoints include the following:

1. *Percent change from baseline in total seizure frequency per 28 days for each (DS and LGS) cohort.*
2. *Percent change from baseline in convulsive seizure frequency (DS) per 28 days.*
3. *Percent change from baseline in MMD seizure frequency (LGS) per 28 days.*

Subjects rolling over from TAK-935-3001 were diagnosed with DS. Percent change from baseline in convulsive 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 in OLE.

Subjects rolling over from TAK-935-3002 were diagnosed with LGS. Percent change from baseline in major motor drop seizure frequency per 28 days and total seizure frequency per 28 days will be summarized for each 12-week period starting from the first dose date of the OLE.

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

The seizure frequency per 28 days during a specified interval of time and a specified set of seizure types (e.g., convulsive, MMD, all) 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 the any 12 weeks of assessment interval, the subject will not be included in the analysis. Note that the denominator is the same for all types of seizures for a specified interval of time for a given subject.

For all seizure frequency calculations, each uncountable seizure cluster will be assigned a count of 1.

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

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

A listing including patient identifier, study week (interval), seizure frequency, percent change from baseline in seizure frequency will be provided.

6.5.2.2 Effect on the CGI-I and Care GI-I

The CGI-I (Clinician) is a 7-point Likert scale that the investigator uses to rate a subject's improvement in overall seizure control, behavior, safety and tolerability, after the initiation of study drug relative to baseline. The subject 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. The count and percentage of each category will be provided by visit.

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. The subject 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.

The count and percentage of each category (using CGI-I and Care GI-I) will be provided by visit. Responses will be dichotomized as "improvement" (scores 1, 2, and 3) or "no change 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 subjects in the "improvement" category using the Clopper-Pearson (exact) method at each visit.

6.5.2.3 Effect on CGI-I Seizure Intensity and Duration

The CGI-I Seizure Intensity and Duration instrument is used by the parent/caregiver to rate changes in intensity and duration of most impactful seizure type(s) experienced in the past month after start of treatment.

The subject'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 parent/caregiver will complete the CGI-I seizure intensity and duration.

The count and percentage of each category will be provided by visit. Responses will be dichotomized as "improvement" (scores 1, 2, and 3) or "no change 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 subjects in the "improvement" category using the Clopper-Pearson (exact) method at each visit.

6.5.2.4 Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregivers

The CGI-I Nonseizure Symptoms instrument includes 3 single-item assessments that the investigator uses to rate improvement in the caregiver-identified symptoms and impacts in select nonseizure domains (including communication, alertness, and disruptive behaviors) since initiating the study drug. The subject 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.

The count and percentage of each category will be provided by visit. Responses will be dichotomized as "improvement" (scores 1, 2, and 3) or "no change 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 subjects in the "improvement" category using the Clopper-Pearson (exact) method at each visit.

6.5.2.5 Effect on 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, positive emotions, negative emotions, social interaction, leisure and the outdoors, and independence.

Each QI-Disability item is rated on a Likert scale of: Never, Rarely, Sometimes, Often, and Very Often. Responses in the negative emotion domain will be scored on a 0–100-point scale with 0=Very often; 25=Often; 50=Sometimes; 75=Rarely; 100=Never. For all other domains, the opposite convention is used: 0=Never; 25=Rarely; 50=Sometimes; 75=Often; 100=Very often. 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. A higher score implies a better outcome.

The change from baseline (in total score) will be summarized descriptively by visits as a continuous variable. Median and distribution-free 95% CI 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.

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 [redacted]

[redacted]

6.5.3.2 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 and date of the End of Maintenance (or Early Termination) visit as the denominator. The proportion of days when rescue ASM is used will be summarized descriptively.

For this analysis, missing start dates for rescue ASM will be imputed to the first day of the month if day is missing but month and year are known, and to the first day of the year 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 if day is missing but month and year are known, and to the last day of the year 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.

6.5.3.3 [redacted]

[redacted]

[redacted]

[redacted]

6.5.3.4 [redacted]

[redacted]

[redacted]

6.5.3.5 Percent change from baseline in plasma 24HC

Individual plasma 24HC levels will be presented in listings. Plasma 24HC level and percent change from baseline will be summarized descriptively by each visit (for the visits when 24HC samples were collected). 24HC values below lower limit of quantitation (LLOQ) are set to 0 for computing descriptive statistics. Mean percent change from baseline in 24HC over time may be presented graphically.

6.5.3.6 Plasma concentrations of soticlestat and its metabolite(s) at multiple time points

Individual plasma concentration-time data for soticlestat and the soticlestat metabolite(s) will be presented in listings.

6.5.3.7 Soticlestat exposure (PK) – plasma 24HC level (pharmacodynamics) analysis and relationship of PK or pharmacodynamic to efficacy response.

Correlation of change in PD (24HC) exposure and efficacy (percent change in convulsive, percent change in MMD seizure frequency) will be investigated. A scatter plot of 24HC percent change from baseline vs percent change from baseline in seizure frequency (separate scatter plot for convulsive and MMD) per 28 days during the 12 weeks prior to the date of the 24HC assessment will be presented, and Spearman's correlation coefficient will be calculated. If a subject has multiple assessments, the median value will be used for the calculation of correlation.

Exposure-PD analysis may be conducted based on a population PK/PD model, as appropriate and reported separately. The exposure-efficacy analysis may be conducted, as appropriate and reported separately.

6.5.3.8 Qualitative caregiver inputs about the caregiver's and subject's experience (selected sites only).

The qualitative input will be obtained as a sub study of the main study protocol and participating clinical sites will recruit caregivers at the time of enrollment into the main study or at a subsequent study visit. Caregivers must sign a separate inform consent form (ICF) to participate. A caregiver's decision not to participate in the sub study will have no effect on the subject's participation in the main study.

The results will be presented in a separate report.

6.5.3.9 Acceptability and Palatability Questionnaires

The percentage of responses corresponding to each question in the palatability/acceptability assessment will be presented over time by dosage form (tablets swallowed, mini-tablets swallowed, tablets crushed and added to food and drink, mini-tablets crushed and added to food and drink) by age groups (2 to <6 years, 6 to <12 years, 12 to <18 years) based on the mITT population. The questions with a 5-point hedonic scale will be recategorized as <3 (worse than OK) and ≥3 (OK or better). This dichotomous response will be summarized using percentage of respondents with OK or better (≥3). The percentages will be calculated using the number of subjects with assessments at a given time point of assessment.

The Acceptability and Palatability data will be listed.

6.5.3.10 [redacted]

[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.

Descriptive statistics such as 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 two sided 95% CIs will be provided, if deemed necessary. For AEs, counts and percentages will be presented by SOC and PT. Analysis will be carried out based on Safety Analysis Set.

6.6.1 Adverse Events

Reported Adverse Event (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 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.a. The summary tables will include the number 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*

AEs of special interest must be recorded as AEs in the eCRF. An evaluation form along with all other required 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. Each type of adverse event of special interest will be listed.

6.6.3 Other Safety Analysis

6.6.3.1 Incidence of abnormal values for clinical laboratory tests and electrocardiogram (ECG) evaluations

Clinical significance is defined as any variation in vital signs that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

Each laboratory parameter will be classified as low, normal and high relative to the parameter's reference range and will be summarized by shift tables. For shift tables, both central and local lab data will be used. Listings of subjects with abnormal results will be provided.

Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, abnormal clinically significant interpretations, not evaluable and total categories by group specified in Table 6.a.

6.6.3.2 Change from baseline in clinical laboratory tests values, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) and ECG parameters.

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 units (if available). Laboratory data outside of the normal reference range will be indicated in the listings. The listing

will include site number, subject identifier, age, gender, treatment group, study visit, and sample collection date.

Descriptive statistics for the observed and change from baseline values will be presented for quantitative data. Antecedent study baseline will be used for change from baseline. Measurements will be summarized by nominal timepoints. Only central lab data will be used for the descriptive summary table.

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 post-baseline 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, treatment group, 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.

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, treatment group, study visit, and sample collection date.

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

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 2, 3, 4, 5 and 6) 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.b will be used to determine the C-SSRS category of a subject. For each visit, the "Yes" answer to the question with the highest severity rank in Table 6.b will be used to determine the C-SSRS category of a subject.

Table 6.b 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)

Shifts in C-SSRS will be presented as cross-tabulation (baseline versus post-baseline categories as in Table 6.b) 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 and suicidal behavior 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 2.a, Table 6.a.

C-SSRS data will also be listed.

6.6.3.3 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 DS, LGS and overall group only.

6.6.3.4 Absolute value for Tanner Stage for children 6 to 17 years of age during the study

As a part of the physical examination, Tanner staging will be done annually for subjects ages 6 to 17 years during the study (for example, if a subject turned 6 during Year 1, he/she should have Tanner staging assessed at the next visit, and annually, until the end of study). It will not be performed when subjects are younger than 6 years or older than 17 years.

The count and percentage of each stage (stages 1-5) in each category of tanner scale will be provided by age and sex (boys and girls). It will be presented by DS, LGS and overall group only. All data for Tanner stage will be listed. If multiple assessment for each subject at particular age is present, then the very first assessment for that subject will be considered for the analysis.

6.6.3.5 Absolute values for IGF-1 for children 2 to 17 years of age during the study

The values of IGF1 will be summarized descriptively as a continuous variable by age and by sex (male and female). It will be presented by DS, LGS and overall group only. If multiple assessments for a subject at different visits at a particular age are available, then the average of all data for that subject will be used for the summary.

6.6.3.6 Physical Examination

Physical examinations data will be listed.

6.6.3.7 Ophthalmological Evaluations

The parameters, visual acuity, cataract screening, fundoscopic examination and retinal examination in ophthalmological evaluations for each group (as per Table 6.a) will be summarized for baseline and each post-baseline visit. All parameters will be presented by left eye, right eye, both eyes and either eye.

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

All ophthalmological evaluation data will be listed.

6.6.3.8 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. It will be presented by group in a similar fashion as other safety parameter.

All neurological examination data will be listed.

6.6.4 Additional Exploratory 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)[1,2]. 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.

6.6.5 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). 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.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 (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 defined 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 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 <90%, 90% 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 for overall. In addition, seizure diary compliance will be summarized descriptively with the number, and percentage of subjects by 0 to <20%, 20% to < 40%, 40% to < 60%, 40% to < 60%, 60% to < 80%, 80% to ≤ 100%.

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:

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

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

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Please refer to Sections 6.5.3.6 and 6.5.3.7.

Population soticlestat PK modeling based on sparse PK:

The population PK and PK/PD models developed for soticlestat based on the data from phase 1 studies in healthy subjects and phase 2 and phase 3 studies in patients will be updated using data from this study and used to estimate PK and PD parameters. The detailed population analysis approach will be described in a separate data analysis plan before database lock. The results of the population PK and PK/PD modeling will be reported separately. Available ASM information will be included in the population PK and PK/PD analysis, if appropriate.

Additional pharmacokinetic analysis results including pop-PK modelling will be presented in a separate report.

6.7.2 Pharmacodynamic Analysis

Please refer to Section 6.5.3.5. Additional pharmacodynamic analysis results including PK-PD analysis results will be presented in a separate report.

6.7.3 Biomarker Analysis

Not applicable.

6.8 Other Analyses

Not applicable.

6.9 Interim Analyses

Interim data cuts from this ongoing study will be analyzed to support any regulatory submissions. Since there is no hypothesis testing involved, no interim analysis will require spending any type-I error. Any interim analyses of the OLE study performed by the sponsor prior to database lock of the antecedent studies will not include treatment assignments from the antecedent studies or any PK or PD data from either the antecedent or OLE studies, as such data is potentially unblinding for the antecedent studies. Management of such potentially unblinding data is documented separately in a Data Access Management Plan (DAMP).

6.10 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/cj411022.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.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
1.1.3.1	NA	New objectives added. • *Assess the palatability and acceptability of the soticlestat tablets and mini-tablets taken orally, either intact or crushed and mixed with applesauce, yogurt, or other liquid of similar consistency, in children with DS or LGS.* [redacted]	New objectives added as per Protocol Amendment 2.
1.2.1	*Endpoints (older version):* • ***Change from baseline in the Columbia-Suicide Severity Rating Scale (C-SSRS)***	Revised and re-worded endpoints: • *Incidence of abnormal values for clinical laboratory tests and*	Revised endpoints added as per protocol amendment 2

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	categorization based on Columbia Classification Algorithm of Suicide Assessment categories1, 2, 3, 4, and 5 for patients ≥6 years of age. • ***Incidence of clinically significant/abnormal clinical safety laboratory test values, vital signs, and electrocardiogram (ECG) evaluations.*** • ***Change from baseline in safety laboratory test values, vital signs, and ECG evaluations.*** • ***Change from baseline in height and weight for all age groups, and in absolute value for Tanner stage for children 6 to 17 years and insulin-like growth factor 1 (IGF-1) for children 2 to 17 years of age during the study.***	*electrocardiogram (ECG) evaluations.* • *Change from baseline in clinical laboratory tests values, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) and ECG parameters.* • *Change from baseline in height and weight for all age groups.* • *Absolute value for Tanner stage for children 6 to 17 years of age during the study.* • *Absolute values for IGF-1 for children 2 to 17 years of age during the study*	
1.2.3	NA	New endpoints added. • *Acceptability and palatability questionnaires* [redacted]	New endpoints added as per protocol amendment 2.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
2.0 4.0	Approximately **376** male and female pediatric and adult subjects from the 2 antecedent phase 3 studies will be rolled over into this study	Approximately 400 male and female pediatric and adult subjects from the 2 antecedent phase 3 studies will be rolled over into this study	Updated total subjects from 376 to 400 as mentioned in protocol amendment 2.
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 ITT (mITT) 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 ITT (mITT) analysis set.	Updated as mentioned in protocol amendment 2.
6.2	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.	Significant protocol deviations will be summarized by site and overall based on the ITT analysis set and 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.	Additional clarification added.
6.3.3	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	Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0 or higher) 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 table will include number and percentages of subjects. SOCs will be sorted in alphabetical order, while preferred terms will be sorted in decreasing	Added “concurrent medical conditions” and giving abbreviation of MedDRA with version number. Replaced word “summary” with “table” for clarification.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	will only be counted once within a particular class even if he/she has multiple conditions/symptoms.	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.	
6.4.1 6.4.2	NA	Added Content: The highest available ATC level will be reported if ATC 4 level is not available.	Additional information needed for clarity.
6.4.2	Concomitant medications will be summarized by ATC class level 2, ATC class level 4, and preferred term. Concomitant ASMs will also be summarized by ATC class level 4, and preferred term. 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 ASMs and concomitant anti-seizure rescue medications will also be summarized by ATC class level 4, and preferred term. Prior and concomitant medications will be listed with prior medications flagged. Similarly, prior and concomitant AEDs will be listed with prior medications flagged.	Added "concomitant anti-seizure rescue medications" for detailed clarification.
6.5.2.1	NA	Added Content: For all seizure frequency calculations, each uncountable seizure cluster is given a count of 1.	Added sentence for clarification for seizure frequency calculation for uncountable seizures.
6.5.2.2 6.5.2.3 6.5.2.4	no **improvement** or worse (scores 4, 5, 6, and 7)	no change or worse	Replaced "no improvement" to "no change" for better clarity.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.5.3.4	[redacted]	[redacted]	[redacted]
6.5.3.5	Individual plasma 24HC levels will be presented in listings **and summarized descriptively per nominal time points. Percent change from baseline will be summarized descriptively by nominal time point.** 24HC values below lower limit of quantitation (LLOQ) are set to 0 for computing descriptive statistics. Mean percent change from baseline in 24HC over time may be presented graphically.	Individual plasma 24HC levels will be presented in listings. Plasma 24HC level and percent change from baseline will be summarized descriptively each visit (for the visits when 24HC samples were collected). 24HC values below lower limit of quantitation (LLOQ) are set to 0 for computing descriptive statistics. Mean percent change from baseline in 24HC over time may be presented graphically.	Updated the sentence as the samples are collected sparsely.
6.5.3.6	Individual plasma concentration-time data for soticlestat and the soticlestat metabolite(s) will be presented in listings **and summarized descriptively per nominal time points will be reported.**	Individual plasma concentration-time data for soticlestat and the soticlestat metabolite(s) will be presented in listings.	Removed summary tables and mean graphics as samples are collected sparsely, hence summary tables and figures by visit will not be appropriate to present.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	Mean plasma concentrations over time will be presented graphically. Concentrations that are reported as below the lower limit of quantitation (LLOQ) will be assigned a value of 0 for calculation of summary statistics.		
6.5.3.7	Correlation of change in PD (24HC) exposure and efficacy (percent change in convulsive or MMD seizure frequency, **as appropriate)** will be investigated. A scatter plot of 24HC percent change from baseline vs percent change from baseline in **convulsive** seizure frequency per 28 days during the 12 weeks prior to the date of the 24HC assessment will be presented, and **Pearson** correlation will be calculated. Similar analysis will be carried out for MMD seizures.	Correlation of change in PD (24HC) exposure and efficacy (percent change in convulsive, percent change in MMD seizure frequency) will be investigated. A scatter plot of 24HC percent change from baseline vs percent change from baseline in seizure frequency (separate scatter plot for convulsive and MMD) per 28 days during the 12 weeks prior to the date of the 24HC assessment will be presented, and Spearman's correlation coefficient will be calculated. If a subject has multiple assessments, the median value will be used for the calculation of correlation.	Removed "e.g. convulsive" as seizure types are already mentioned in parenthesis after "efficacy". Modified: Spearman's correlation coefficient will be computed in place of Pearson's correlation. Updated: Median (seizure and 24HC data collected over time for each subject) will be computed for each subject in order to calculate correlation coefficient.
6.5.3.9	NA	New analysis section added	New endpoint analysis added.
6.5.3.10	[redacted]	[redacted]	[redacted]

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.6.2	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* *AEs of special interest must be recorded as AEs in the eCRF. An evaluation form along with all other required 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 6.6.1.** **Potential drug-drug interaction between soticlestat and perampanel leading to increased seizure frequency:** **The general algorithm is to find the start of the overlap period between the two drugs and compare all seizure frequency in the overlap period against the period before. The following PT terms (Seizure, Seizure cluster, Exacerbation of**	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* *AEs of special interest must be recorded as AEs in the eCRF. An evaluation form along with all other required 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. Each type of adverse event of special interest will be listed.	Only CRF collected AESIs will be summarized as the main output for AESI.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	disease) can be considered when subject is taking perampanel or fycompa concomitantly in order to identify potential drug-drug interaction between soticlestat and perampanel. **The following MedDRA terms (PT) will be used to identify following AESIs.** **Cataracts: Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Toxic cataract** **Psychosis: Psychotic disorder, Acute psychosis, Transient psychosis, Reactive psychosis, Rebound psychosis.**		
6.6.3.1	Shift table categories have been redefined.	Modify C-SSRS shift table categories. Refer to Table 6.b for details on categories.	Updated categories for shift tables allow more appropriate clinical interpretation.
6.6.3.2	Incidence **of clinically significant**/abnormal **safety laboratory test** values, vital signs, and electrocardiogram (ECG) evaluations Each laboratory parameter will be classified as low, normal and 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 for each treatment with shift tables**. Listings of subjects with	Revised endpoint: Incidence of abnormal values for clinical laboratory tests and electrocardiogram (ECG) evaluations. Removed content: The number and percentage of subjects with shifts in clinical laboratory parameters will be summarized. Laboratory abnormalities for each treatment with shift tables. Revised analysis: For shift tables, both central and local lab data will be used	Corrected endpoint title as per Protocol Amendment 2. Some sentences reframed for better clarity in analyses.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	abnormal results will be provided.	Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, abnormal clinically significant interpretations, not evaluable and total categories by group specified in Table 6.a	
6.6.3.3	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 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 post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations with missing, if applicable, and total categories, as applicable, by group specified in Table 6.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	Descriptive statistics for the observed and change from baseline values will be presented for quantitative data. Antecedent Study baseline will be used for change from baseline. Measurements will be summarized by nominal timepoints. Only central lab data will be used for the descriptive summary table. 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 (QTcB) will be categorized as: <30 msec, 30 msec – 60 msec and > 60 msec.	Added “for quantitative data” for better clarity. Also added that only “central” data will be used for analyses of summary tables. Removed ECG shift table from the section as already it is mentioned in section 6.6.3.2 Removed “Missing” from the categories as it is not required and informative to be presented in OLE study.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	categorized as: <450 msec, 450 msec – <480 msec, 480 msec – 500 msec and > 500 msec **and Missing**. The change from baseline values (ΔQTcF) will be categorized as: <30 msec, 30 msec – 60 msec and > 60 msec **and Missing,**		
6.6.3.4	The change from baseline for height and weight will be summarized descriptively by visit **as a continuous variable for all age groups.** The count and percentage of each stage (stages 1-5) in each category of tanner scale **for boys and tanner scale for girls** will be provided by age **and by visit (including baseline)**. It will be presented by DS, LGS and overall group only. The values of IGF1 will be summarized descriptively as a continuous **variable by visit (including baseline)** by age and by sex (male and female). It will be presented by DS, LGS and overall group only.	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. The count and percentage of each stage (stages 1-5) in each category of tanner scale will be provided by age and sex (boys and girls). It will be presented by DS, LGS and overall group only. All data for tanner stage will be listed. If multiple assessment for each subject at particular age is present, then the very first assessment for that subject will be considered for the analysis. The values of IGF1 will be summarized descriptively as a continuous variable by age and by sex (male and female). It will be presented by DS, LGS and overall group only. If multiple assessments for a subject at different visits at a particular age is available, then the average of all data for that subject will be used for the summary.	Updated analysis for height weight from each age to two groups for better clinical interpretation. Presenting Tanner Stage and IGF-1 by age and sex, hence removed visit. Additional clarification added.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.6.3.6	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 in 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.	The parameters, visual acuity, cataract screening, fundoscopic examination and retinal examination in ophthalmological evaluations for each group (as per Table 6.a) will be summarized for baseline, and each post-baseline visit. All parameter categories will be summarized by left eye, right eye, both eyes and either eye. The number and percentages of subjects having significantly declined in visual acuity will be provided over time. Similarly, subjects having anterior or posterior lens opacities in cataract screening, subjects having retinal examination assessed as abnormal, and subjects having optic nerve exam as abnormal in fundoscopic examination will be summarized.	Added "retinal examination" as categories. Added clarification on presentation of the data.
6.6.3.7	NA	All neurological examination data will be listed.	Added to provide listings.
6.6.4	NA	New section added.	To explore growth trends in observed heights and weights for subjects 18 years old or younger.
6.6.5	Extent of exposure (in **weeks**) of study medication is defined as (date of last dose – date of first dose +1)/**7**. In addition, number and percentage of subjects will be provided by **dose level (1. 2. 3) at each visit.**	Extent of exposure (in days) of study medication is defined as (date of last dose – date of first dose +1). In addition, number and percentage of subjects 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	Presenting exposure in days instead of weeks, hence removed (in denominator) by 7 for calculation Clarification for presenting dose levels are provided.

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
		period. If there are multiple doses with the longest duration, the highest dose will be used as the maintenance dose.	
6.6.5	Using the **electronic** daily seizure and medication diary.	Using the daily seizure and medication diary.	Removed electronic as seizure diary is collected through paper.
6.6.5	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%)** Number, and percentage of subjects with seizure diary compliance will be summarized by **<80% and >=80%.**	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 <90%, 90% to <100%, 100% to < 120% and ≥ 120%) Study medication compliance will also be summarized as a continuous variable using descriptive statistics for overall. In addition, seizure diary compliance will be summarized descriptively with the number, and percentage of subjects by 0 to <20%, 20% to < 40%, 40% to < 60%, 40% to < 60%, 60% to < 80%, 80% to ≤ 100%.	Updated the categories for study medication and seizure diary compliance.
7.0	NA	Added References to support section 6.6.3	Added as reference.
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 midpoint technique (using study days) will be used to	Updated content 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.	Updated for more clarity in visit windowing which is considered for all the visits regardless of scheduled and unscheduled. Removed second paragraph as all data will be used for mapping into the analysis

Table 9.a Summary of Changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	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.**		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.
9.2.5	NA	New section added	New rules added for missing seizure diary data and how to handle them.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

9.2.2 Definition of Baseline

Unless otherwise specified, baseline is defined as the baseline of the antecedent study.

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, Early Termination (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.

If central and local laboratory data are available on the same day, central laboratory data will be used. If, after prioritizing central lab data, there are multiple lab measurements recorded on the same day, then the worst among these measurements will be used.

Endpoints: C-SSRS, CGI-I, Care GI-I, QI-Disability, [redacted]

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.

9.2.5 Handling of Seizure Diary Data

Seizure data are collected via the seizure diary, including the date of seizure, and the Yes or No response with number of occurrences.

- Only completed records (available records with seizure occurrence date, seizure free date, seizure type, number of seizures during event, etc.) will be included in the seizure data summaries and analyses.
- If the answer to the question “Did any seizures occur?” is “No”, but the record contains complete information on seizures for that particular day (such as seizure occurrence date, seizure type, number of seizures, etc.) then the seizures recorded will be used for summary and that particular day will not be considered as a seizure free day.

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-935-3003_ENDYMION_2_Amend1
Title: TAK-935-3003_ENDYMION_2_SAP_Amend1

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