Statistical Analysis Plan

NCT Number : NCT04938427

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Adult Subjects With Lennox-Gastaut Syndrome (LGS)

Study Number: TAK-935-3002

Document Version and Date: Amendment 1.0, 05 March 2024

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-935-3002 (SKYWAY)

Study Title: A 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)

Phase 3

Version: Amendment 1

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Based on:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original	29-Mar-22	Not applicable
Amendment 1	8-Mar-2024	Add updates aligned with protocol amendment 2, clarifications, and additional sensitivity and exploratory analyses

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ABBREVIATIONS

24HC	24S-hydroxycholesterol
ADaM	analysis data model
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ASM	antiseizure medication
BID	twice daily
Care GI-I	Caregiver Global Impression of Improvement
CGI-I	Clinical Global Impression of Improvement
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EQ-VAS	Visual Analogue Scale
GCP	good clinical practice
IEC	institutional review board
IRB	independent ethics committee
ITT	intent-to-treat
LLOQ	lower limit of quantification
LGS	Lennox-Gastaut syndrome
LOCF	last observation carried forward
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MMD	major motor drop
mITT	modified intent-to-treat
MNAR	missing not at random
OLE	open-label Extension
QI-Disability	Quality of Life Inventory-Disability
PBO	placebo
PD	pharmacodynamic
PEG	percutaneous endoscopic gastrostomy
PK	pharmacokinetic
PT	Preferred Term
PTE	pretreatment event

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SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	study data tabulation model
SF	seizure frequency
SOC	standard of care
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
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 reducing major motor drop (MMD) seizure frequency as add-on therapy to standard of care (SOC) as compared with placebo during the full treatment period (titration + maintenance).*

For European Medicines Agency (EMA) registration:

- *To assess the efficacy of soticlestat in reducing MMD seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.*

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1.1.2 Secondary Objectives

To assess the following in subjects taking soticlestat as compared with placebo during the full treatment period, unless otherwise noted:

- *Proportion of treatment responders defined as those with ≥50% reduction in MMD seizures from baseline during the maintenance period and the full treatment period.*
- *Effect on total seizure frequency of all seizure types during the maintenance period and the full treatment period.*
- *Change from baseline in proportion of MMD seizure-free days.*
- *Longest MMD seizure-free interval.*
- *Number of days when rescue antiseizure medications (ASMs) are used.*
- *Effect on the Clinical Global Impression of Improvement (CGI-I) (clinician) and Caregiver Global Impression of Improvement (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 Quality of Life Inventory-Disability (QI-Disability).*

1.1.3 Additional Objectives

1.1.3.1 Exploratory Objectives

To assess the following in subjects receiving soticlestat as compared with placebo during the full treatment period:

- *Seizure frequency of each seizure type per 28 days.*
- *Health care resource utilization including but not limited to emergency room visits and hospitalizations.*
- *Population PK and correlation of the population PK exposure parameters with PD (plasma 24HC levels) in subjects receiving soticlestat.*
- *Correlation of change in PD (24HC) exposure and efficacy (change in MMD seizure over the full treatment period).*
- *Effect on EQ-5D 5-Level version (EQ-5D-5L) quality of life scale for parents'/caregivers' quality of life.*

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1.1.3.2 Safety Objectives

- *To assess the incidence of TEAEs.*
- *To assess the incidence of abnormal clinical laboratory values and electrocardiogram (ECG) evaluations.*
- *To assess change from baseline in clinical laboratory values, vital signs, ECG parameters, and Columbia-Suicide Severity Rating Scale (C-SSRS) responses.*
- *To assess the incidence of new seizure types arising during soticlestat treatment that are not identified at the time of screening (by history) or during prospective baseline.*

1.2 Endpoints

1.2.1 Primary Endpoints

- *Percent change from baseline in MMD seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the full treatment period.*

For EMA registration:

- *Percent change from baseline in MMD seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the maintenance period.*

1.2.2 Secondary Endpoints

To assess the following in subjects receiving soticlestat as compared with placebo during the full treatment period, unless otherwise noted:

- *Proportion of responders defined as those with ≥50% reduction from baseline in MMD seizures during the maintenance period and the full treatment period.*
- *Responder analysis of the proportion of subjects with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, and >75% to ≤100% reduction from baseline in MMD seizures in a cumulative response curve.*
- *Care GI-I (caregiver).*
- *CGI-I (clinician).*
- *CGI-I Nonseizure Symptoms.*
- *Change in QI-Disability score.*
- *CGI-I Seizure Intensity and Duration.*
- *Percent change from baseline in frequency of all seizures per 28 days during the maintenance period and the full treatment period.*
- *Percent change from baseline in MMD seizure frequency per 28 days during the maintenance period.*
- *Change from baseline in proportion of MMD seizure-free days.*
- *Longest MMD seizure-free interval.*
- *Number of days when rescue ASM is used.*

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1.2.3 Exploratory Endpoints

To assess the following in subjects receiving soticlestat as compared with placebo during the full treatment period:

- *Percent change from baseline in frequency per 28 days of each seizure type identified at the time of screening or baseline.*
- *Health care resource utilization including but not limited to emergency room visits and hospitalizations.*
- *Soticlestat exposure-PD (plasma 24HC level) and efficacy response analysis.*
- *Percent change from baseline in plasma 24HC.*
- *Plasma concentrations of soticlestat and the soticlestat metabolite(s) at multiple time points.*
- *Population soticlestat PK modeling based on sparse PK.*
- *Change in EQ-5D-5L and EQ-5D visual analogue scale (EQ VAS) scores.*

1.2.4 Safety Endpoints

- *Incidence of TEAEs.*
- *Incidence of abnormal clinical laboratory values and ECG evaluations.*
- *Change from baseline in clinical laboratory values, vital signs, ECG parameters, and C-SSRS responses.*
- *Incidence of new seizure types arising post–study treatment initiation.*

1.3 Estimands

1.3.1 Primary Estimand

The primary estimand is the treatment effect of soticlestat compared to Placebo during the Full Treatment Period in the targeted patient population. For EMA registration the treatment effect during the Maintenance Period is of primary interest. The defining attributes of the estimand are provide in Table 1.a.

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Table 1.a Attributes of the Primary Estimand

Treatment	Population	Variable (or Endpoint)	Strategy for Addressing Intercurrent Events	Population-Level Summary
Soticlestat or placebo regimen added to SOC. The regimen consists of a 4-week Titration Period followed by a 12-week Maintenance Period, and may include rescue medication.	Targeted patient population for approval as defined through the inclusion/exclusion criteria	Percent change from baseline in MMD seizure frequency per 28 days during the Full Treatment Period. For EMA registration: Percent change from baseline in MMD seizure frequency per 28 days during the Maintenance Period.	The treatment policy strategy will be used to address all intercurrent events. The anticipated intercurrent events include early discontinuation of study drug for any reason, and addition of rescue medication or other concomitant therapies or change in background antiseizure therapy, regardless of whether allowed by protocol. Seizure diary data collected after intercurrent events up to the end of the Full Treatment Period will be included in the calculation of the primary endpoint. For EMA registration: The principal stratum strategy will be used to	The medians of the variables will be estimated for each treatment group, and comparison between treatment groups will be based on the location shift between populations.

Table 1.a Attributes of the Primary Estimand

Treatment	Population	Variable (or Endpoint)	Strategy for Addressing Intercurrent Events	Population-Level Summary
			address the intercurrent event of discontinuation of study drug prior to entering the Maintenance Period. Other intercurrent events will be handled with the treatment policy strategy as described above.	

1.3.2 Secondary Estimands

The estimands corresponding to secondary objectives that are subject to hypothesis testing are defined in Table 1.b. A gatekeeping procedure will be used to test the hypotheses in the order listed below. For details, please refer to Sections 3.1 and 3.2.

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Table 1.b Attributes of Secondary Estimands

Objective	Attributes
Note: The following are to be assessed in subjects taking soticlestat as compared with placebo during the Full Treatment Period, unless otherwise noted	Note: For all secondary study objectives listed here, the treatment and population for the corresponding estimands are the same as for the primary estimand (Table 1.a)
Secondary #1: *The proportion of treatment responders defined as those with ≥50% reduction in MMD seizures from baseline during* the Full Treatment Period. For EMA registration: *Proportion of treatment responders defined as those with ≥50% reduction in MMD seizures from baseline during* the Maintenance Period.	**Variable:** Binary variable indicating whether the subject is a treatment responder during the Full Treatment Period (or Maintenance Period for EMA registration). **Strategy for Addressing Intercurrent Events:** All anticipated intercurrent events will be addressed using the treatment policy strategy. For EMA registration: The principal stratum strategy will be used to address the intercurrent event of discontinuation of study drug during the Titration Period. Other intercurrent events will be handled with the treatment policy strategy. Population-Level Summary: The number of responders will be summarized as a proportion for each treatment group, and comparison between treatment groups will be based on the odds ratio.
Secondary #2 *Effect on the Caregiver Global Impression of Improvement (Care GI-I).*	**Variable:** Response on the 7-point Care GI-I scale at the end of the Full Treatment Period.

Table 1.b Attributes of Secondary Estimands

Objective	Attributes
Note: The following are to be assessed in subjects taking soticlestat as compared with placebo during the Full Treatment Period, unless otherwise noted	Note: For all secondary study objectives listed here, the treatment and population for the corresponding estimands are the same as for the primary estimand (Table 1.a)
	Strategy for Addressing Intercurrent Events: All anticipated intercurrent events will be addressed using the treatment policy strategy. Population-Level Summary: The number of responses in each category of the scale will be summarized using proportions for each treatment group, and comparison between treatment groups will be based on the odds ratio.
Secondary #3 *Effect on the Clinical Global Impression of Improvement* (CGI-I) (clinician).	**Variable:** Response on the 7-point CGI-I scale at the end of the Full Treatment Period. **Strategy for Addressing Intercurrent Events:** All anticipated intercurrent events will be addressed using the treatment policy strategy. **Population-Level Summary:** The number of responses in each category of the scale will be summarized using proportions for each treatment group, and comparison between treatment groups will be based on the odds ratio.
Secondary #4 *Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregiver.*	**Variable:** Responses on the three domains (testing order will be: alertness communication, and disruptive behaviors) of the CGI-I Nonseizure Symptoms scale at the end of the Full Treatment Period. **Strategy for Addressing Intercurrent Events:** All anticipated intercurrent events will be addressed using the treatment policy strategy. **Population-Level Summary:** The number of responses in each category of the scale within each domain will be summarized for each treatment group using proportions, and comparison between treatment groups per domain will be based on the odds ratio.
Secondary #5 *Effect on Quality of Life Inventory-Disability (QI-Disability).*	**Variable:** Change from baseline in QI-Disability total score at the end of the Full Treatment Period. **Strategy for Addressing Intercurrent Events:** All anticipated intercurrent events will be addressed using the treatment policy strategy. **Population-Level Summary:**

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Table 1.b Attributes of Secondary Estimands

Objective	Attributes
Note: The following are to be assessed in subjects taking soticlestat as compared with placebo during the Full Treatment Period, unless otherwise noted	Note: For all secondary study objectives listed here, the treatment and population for the corresponding estimands are the same as for the primary estimand (Table 1.a)
	The mean changes from baseline to the end of the Full Treatment Period in QI-Disability total score will be estimated for each treatment group, and comparison between treatment groups per domain will be based on the difference in group means.
Secondary #6 *Effect on CGI-I Seizure Intensity and Duration.*	**Variable:** Response on the 7-point CGI-I Seizure Intensity and Duration scale at the end of the Full Treatment Period. **Strategy for Addressing Intercurrent Events:** All anticipated intercurrent events will be addressed using the treatment policy strategy. **Population-Level Summary:** The number of responses in each category of the scale will be summarized using proportions for each treatment group, and comparison between treatment groups will be based on the odds ratio.

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2.0 STUDY DESIGN

2.1 Overall Study Design

This is a phase 3, global, multicenter, 1:1 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in pediatric and adult subjects with LGS. The treatment period is approximately 16 weeks. The total duration of the study is approximately 25 weeks for subjects who complete the study and choose not to roll over to the open-label extension (OLE) study. For those who roll over to the OLE study, the study duration is 3 weeks shorter.

Approximately 234 male and female pediatric and adult subjects will be randomized.

Randomization of subjects in the study will be stratified by age group and country. The strata for stratification by age group will be: ≤6 years and >6 years; these age-group randomization strata will be included as a fixed effect factor in the statistical model for the analysis of the primary endpoint.

The strata for stratification by country will be: China, Japan, and the rest of the world. This country stratification is planned to be implemented for an administrative reason and therefore will not be included in the primary analysis model.

This study consists of the following periods:

- *4- to 6-week screening/baseline period. The minimum duration for screening is 28 days (ie, Visit 2/Day 0 cannot occur earlier than 29 days after screening).*
- *16-week treatment period.*

4-week titration period.

12-week maintenance period.

- *1-week taper period for those discontinuing study drug, followed by a 2-week safety follow-up visit or phone call.*

This is a 2-arm study. All subjects will be randomized at a 1:1 ratio to receive SOC plus 1 of the following adjunctive therapies: soticlestat or placebo.

Soticlestat or matching placebo added to current antiseizure therapy, will be administered orally BID with or without food or via gastrostomy tube (G-tube) or low-profile gastric tube (MIC-KEY button). 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 schematic of the study design is shown in Figure 2.a. *A schedule of assessments is listed in* protocol *Appendix A.*

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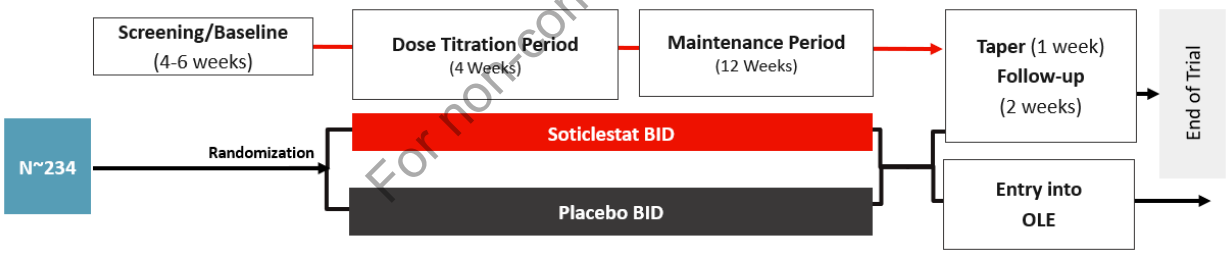
Figure 2.a Schematic of Study Design



BID: twice daily; OLE: open-label extension.

All doses will be blinded and will undergo the same titration scheme, with the same number and type of tablets (mini-tablets or tablets). Subjects randomized to placebo will undergo a mock titration to ensure the blind is maintained (see tables below*).*

The total daily dose of study drug (either placebo or soticlestat) will be calculated based on body weight at Visit 1 (screening visit) and given BID starting on the morning after Visit 2/Day 0 (ie, on study Day 2) or on the day after receiving study medication. The dosing schedules by weight are show in Table 2.a *through* Table 2.d.*. (see tables below). The minimum dose allowed during the study is 100 mg BID (weight-based dosing <45 kg.) Subjects who cannot tolerate the minimal dose will be discontinued from the study. Subjects weighing <45 kg will be dispensed 20 mg mini-tablets or matching placebo. Subjects weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets, or matching placebo.*

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

Treatment Arm	***10 to <15 kg Weight Reference Dose***					
	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***
Soticlestat	*40 mg BID*	*2 mini tabs soticlestat BID*	*60 mg BID*	*3 mini tabs soticlestat BID*	*100 mg BID*	*5 mini tabs soticlestat BID*
PBO	*---*	*2 mini tabs PBO BID*	*---*	*3 mini tabs PBO BID*	*---*	*5 mini tabs PBO BID*

BID: twice daily; No.: number; PBO: placebo.

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

Treatment Arm	***15 to <30 kg Weight Reference Dose***					
	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***
Soticlestat	*60 mg BID*	*3 mini tabs soticlestat BID*	*120 mg BID*	*6 mini tabs soticlestat BID*	*200 mg BID*	*10 mini tabs soticlestat BID*
PBO	*---*	*3 mini tabs PBO BID*	*---*	*6 mini tabs PBO BID*	*---*	*10 mini tabs PBO BID*

BID: twice daily; No.: number; PBO: placebo.

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

Treatment Arm	***30 to <45 kg Weight Reference Dose***					
	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***
Soticlestat	*80 mg BID*	*4 mini tabs soticlestat BID*	*140 mg BID*	*7 mini tabs soticlestat BID*	*200 mg BID*	*10 mini tabs soticlestat BID*
PBO	*---*	*4 mini tabs PBO BID*	*---*	*7 mini tabs PBO BID*	*---*	*10 mini tabs PBO BID*

BID: twice daily; No.: number; PBO: placebo.

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

Treatment Arm	***≥45 kg Weight Reference Dose***					
	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***
Soticlestat	*100 mg BID*	*1 tab soticlestat BID OR 5 mini tabs soticlestat BID*	*200 mg BID*	*2 tabs soticlestat BID OR 10 mini tabs soticlestat BID*	*300 mg BID*	*3 tabs soticlestat BID OR 15 mini tabs soticlestat BID*
PBO	*---*	*1 tab PBO BID OR 5 mini tabs PBO BID*	*---*	*2 tabs PBO BID OR 10 mini tabs PBO BID*	*---*	*3 tabs PBO BID OR 15 mini tabs PBO BID*

BID: twice daily; No.: number; PBO: placebo.

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2.2 Dose Titration Period (4 Weeks)

Subjects will take the first dose of study drug (Dose 1) the day after the study medication is received. Approximately 7 days after initiating study medication, if there are no tolerability issues, study drug dose will be increased to Dose 2. After approximately 7 days on Dose 2, if there are no tolerability issues, study drug dose will be increased to Dose 3. If the subjects do not experience any tolerability issues, they will continue on Dose 3 for the remainder of the titration period. Subjects will only be allowed to increase their dose within the 4-week titration period before entering the 12-week maintenance period. Decrease in dose level is allowed during the titration period 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 each dose escalation to assess safety and tolerability of the study drug. The final dose tolerated by the end of the 4-week titration period should be maintained until the end of the maintenance period, unless tolerability issues arise.

2.3 Maintenance Period (12 Weeks)

The dose level at the end of the titration period will be maintained until the end of the maintenance period (dose increases are not permitted); 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 of 100 mg BID will be discontinued from treatment. Dose changes during the maintenance period are allowed

for safety or tolerability reasons as assessed by the investigator; however, if possible, dose changes will need to be discussed with the medical monitor and/or the sponsor.

2.4 Study Discontinuation/Completion

At Visit 11/early termination, subjects will have the option to enroll in the OLE study as per that study's inclusion/exclusion criteria.

Subjects who enroll in the OLE study on the same day as Visit 11/early termination will take their final dose of double-blind study drug in the evening of the day of Visit 11/early termination and should continue to record seizures in the seizure diary until midnight of the day of Visit 11/early termination, at which time they will exit the study.

Subjects who do not roll over to the OLE study on the same day as Visit 11/early termination will take their final dose of double-blind study drug in the morning of Visit 11/early termination, followed by a 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) approximately every 3 days until the study drug dose is discontinued. The subject/parent or caregiver should continue to record seizures in the seizure diary until the safety follow-up phone call, which will occur approximately 14 days after the last dose of study drug. After completion of the safety follow-up phone call, the subject will exit the study.

Subjects/parents or caregivers who choose to enroll in the OLE study after Visit 11/early termination will continue the taper procedure until the investigator confirms eligibility for the OLE study; the subject will then exit the study and roll over to the OLE study.

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3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

The study objectives that will be subjected to statistical hypothesis testing are listed below, along with corresponding statistical null hypotheses and statistical criteria for a positive outcome for each objective. A gatekeeping procedure will be used to test the hypotheses in the order listed below. Thus a positive outcome for a hypothesis is contingent on positive outcomes for the preceding hypotheses.

Table 3.a Statistical Hypotheses

Study objective	Statistical null hypothesis	Criteria for positive outcome
Primary: *To assess the efficacy of soticlestat in reducing MMD seizure frequency as add-on therapy to standard of care (SOC) as compared with placebo during the full treatment period (titration + maintenance).* *For EMA registration:*	The distribution of percent change from baseline in MMD seizure frequency per 28 days during the Full Treatment Period (Maintenance Period for EMA registration) is equal between the soticlestat and placebo treatment populations conditional on age stratum (≤6 years, >6 years).	Statistically significant result from the test of no treatment effect based on the primary rank ANCOVA model including treatment group and age stratum as factors, and rank of baseline seizure frequency per 28 days as a covariate.

Table 3.a Statistical Hypotheses

Study objective	Statistical null hypothesis	Criteria for positive outcome
To assess the efficacy of soticlestat in reducing MMD seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.		
Secondary #1: *Proportion of treatment responders defined as those with ⩾50% reduction in MMD seizures from baseline during* the full treatment period. For EMA registration: *Proportion of treatment responders defined as those with ⩾50% reduction in MMD seizures from baseline during* the maintenance period.	The odds of treatment response are equal between the soticlestat and placebo treatment populations conditional on age stratum.	Statistically significant result from the test of no treatment effect based on the Cochran-Mantel-Haenszel test stratified by age stratum.
Secondary #2 *Effect on the Caregiver Global Impression of Improvement (Care GI-I).*	The cumulative odds of a response in each Care CG-I ordinal response category at the end of the Full Treatment Period is equal between the soticlestat and placebo treatment populations conditional on age stratum.	Statistically significant result from the test of no treatment effect based on a cumulative logit model with treatment group and age stratum as factors.
Secondary #3 *Effect on the Clinical Global Impression of Improvement* (CGI-I) (clinician).	The cumulative odds of a response in each CCG-I ordinal response category at the end of the Full Treatment Period is equal between the soticlestat and placebo treatment populations conditional on age stratum	Statistically significant result from the test of no treatment effect based on a cumulative logit model with treatment group and age stratum as factors.
Secondary #4 *Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregiver.*	The cumulative odds of a response in each CGI-I Nonseizure Symptoms ordinal response category in the Alertness domain, Communication domain, and the Disruptive Behaviors domain at the end of the Full Treatment Period is equal between the soticlestat and placebo treatment populations conditional on age stratum.	Statistically significant results from the tests of no treatment effect in all three domains based on a separate cumulative logit model for each domain with treatment group and age stratum as factors. Testing (sequential) order will be as follows: alertness, communication, and disruptive behaviors. Statistical significance of individual domains within the hierarchy can be asserted with global type 1 error control provided all preceding tests are significant, but statistical significance of the full endpoint

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Table 3.a Statistical Hypotheses

Study objective	Statistical null hypothesis	Criteria for positive outcome
		consisting of all 3 domains of CGI-I Nonseizure Symptoms, can only be asserted if all 3 domains are statistically significant.
Secondary #5 *Effect on Quality of Life Inventory-Disability (QI-Disability).*	The change from baseline in QI-Disability total score at the end of the Full Treatment Period is equal between the soticlestat and placebo treatment populations conditional on age stratum.	Statistically significant result from the test of no treatment effect at the end of treatment visit based on an MMRM model with treatment group, visit, age stratum, and treatment by visit interaction as fixed effects.
Secondary #6 *Effect on CGI-I Seizure Intensity and Duration.*	The cumulative odds of a response in each CGI-I Seizure Intensity and Duration ordinal response category at the end of the Full Treatment Period is equal between the soticlestat and placebo treatment populations conditional on age stratum.	Statistically significant result from the test of no treatment effect based on a cumulative logit model with treatment group and age stratum as factors.

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3.2 Multiplicity Adjustment

The global type 1 error will be controlled at 2-sided 5% level using a hierarchical gatekeeping procedure on the primary and the secondary endpoints mentioned in Sections 1.3.2 and 3.1. Hypotheses will be tested in the order described in Section 3.1. The gatekeeping procedure only requires testing hypotheses for the corresponding regulatory agencies. For example, the gatekeeping procedure does not require testing EMA registration hypotheses for other regulatory agencies.

4.0 SAMPLE-SIZE DETERMINATION

The study will randomize a total of approximately 234 subjects at a 1:1 ratio to receive 1 dose level of soticlestat or placebo, resulting in approximately 117 subjects per arm.

The primary endpoint for this study is the percent change from baseline in MMD seizure frequency per 28 days. The definition for MMD is different for this study than for ELEKTRA, however, the variability of this endpoint is assumed to be the same. This leads to an assumption that the pooled SD of the percent change from baseline in MMD seizure frequency is 65%.

A difference of 26.5% in mean percent reduction in MMD seizure frequency between treatments is an appropriate target. A sample size of 117 subjects per treatment arm will provide at least 85% power at a two-tailed 5% significance level to detect a difference of 26.5% in mean percent reduction in seizure frequency between treatments using the Wilcoxon rank-sum test, assuming the pooled SD above of 65%.

5.0 ANALYSIS SETS

5.1 ITT Analysis Set

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

5.2 mITT Analysis Set

All randomized 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.

5.3 Safety Analysis Set

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

5.4 Pharmacokinetic (PK) 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 Pharmacodynamic (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.

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6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All hypothesis tests and confidence intervals (CIs) will be 2-sided. A significance level of 0.05 will be used for all statistical testing, unless otherwise stated. All p-values reported will be 2-tailed and rounded to 3 decimal places prior to assessment of statistical significance.

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 treatment group within that 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, 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, minimum, and maximum values will be tabulated.

Descriptive summaries for efficacy, PK, and PD endpoints will be provided by treatment group unless indicated otherwise. Descriptive summaries for safety endpoints will be provided by

treatment group and overall unless indicated otherwise. Descriptive summaries of demographic characteristics, baseline characteristics, medical history and concurrent medical conditions, concomitant medications, ASMs, and concomitant rescue medications will be based on the safety analysis set. The mITT analysis set may also be used if it differs from the safety analysis set. Generally, the ITT analysis set will be used for listings unless indicated otherwise.

All log transformations will be based on natural logarithms.

If a subject is assigned to the wrong age stratum during randomization, the actual age, collected as a part of demographic information, will be used to identify the correct age stratum (≤6 or >6 years) for all summaries and analyses that reference age stratum.

6.1.1 Handling of Treatment Misallocations

If a subject is randomized but takes incorrect treatment, the planned randomized treatment assignment will be used in analyses that are based on the ITT or mITT analysis sets, but the actual treatment the subject received will be used in analyses that are based on the safety, PK, or PD analysis sets.

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6.2 Disposition of Subjects

Disposition of all randomized subjects will be tabulated:

- Subjects randomized
- Subjects randomized but not treated
- Subjects received at least one dose of study drug (denominator)
- Subjects who completed V11
- Subjects who did not roll over to the OLE study
- Subjects who rolled over to the OLE study
- Subjects who prematurely discontinued the study drug
- Subjects who prematurely discontinued study

Primary reasons for discontinuation of study drug or study will be tabulated.

Summaries will be presented by treatment groups (placebo and soticlestat) and overall.

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be listed. If known, a reason for their discontinuation will be listed.

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 treatment group 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.

Screen failure subjects will be summarized descriptively. Primary reasons for failure will be summarized and will be presented in a data listing.

A summary table for all analysis sets will be created. Patients excluded from an analysis set will be listed.

A table will be created summarizing the number of subjects randomized to each country and site.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographic characteristics will be summarized and listed. Variables to be presented include age, stratification age category, sex, ethnicity, and race.

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6.3.2 Baseline Characteristics

Baseline characteristics including disease characteristics and interventions related to DS will be summarized and listed. Variables to be presented include:

- Weight, height, body mass index (BMI)
- Years since diagnosis
- Number of ASMs: categorized as 0, 1, 2, 3 etc.
- MMD seizure frequency during Baseline Period
- All seizure frequency during Baseline Period
- Ketogenic/ modified Atkins Diet
- Vagus nerve stimulation

6.3.3 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see protocol *Section 9.1.13).*

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. These include clinically significant laboratory, ECG, or physical examination abnormalities noted at screening (Visit 1), according to the judgement of the investigator. The condition (ie, diagnosis) should be described and recorded in the eCRF.

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 by treatment group and overall using System Organ Class (SOC) and MedDRA preferred term. 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 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.

Medical history and concurrent medical conditions will be summarized and listed.

6.4 Medication History and Concomitant Medications

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 6 months before signing of informed consent.

All ASMs stopped prior to signing of informed consent should be recorded.

6.4.1 Prior Medications

Any medication stopped prior to first dose of study drug will be considered prior medication.

Prior medication will not be summarized but will be listed with concomitant medications and be identified as "prior" in the listing.

6.4.2 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject/parent or caregiver over the counter. Concomitant medication is not provided by the sponsor. At each study visit, the subject/parent or caregiver will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medications including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF. Documentation will include generic or trade medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

ASMs treatments, artisanal cannabidiol use, VNS settings, and ketogenic diet should not be altered during the study.

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. Only the concomitant medication use will be summarized.

The number and percentage of subjects who took at least 1 medication during the double-blind period as well as the number and percentage of subjects who took each type of medication will be presented for each treatment group. Medications will be listed 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 for all active treatment groups combined.

The list of excluded medications and procedures is provided in protocol *Appendix B.*

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Concomitant medications, concomitant ASMs, and concomitant rescue medications will be summarized. The number and percentage of patients receiving each ASM concomitantly, and each rescue medication concomitantly will be presented as well as the number and percentage of patients with at least 1 concomitant ASM and concomitant rescue medication. ASM listing will also be presented. Summaries and analyses will be based on the data available in electronic data capture (EDC).

Missing or partial dates will not be imputed. Conservatively, a medication or procedure will be classified as concomitant if the available information about the end date is insufficient to determine whether it was stopped before first dose of study drug.

6.5 Efficacy Analysis

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

6.5.1 Primary Endpoint Analysis

6.5.1.1 Derivation of Endpoint

The primary endpoint is:

- *Percent change from baseline in MMD seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the full treatment period.*

For EMA registration:

- *Percent change from baseline in MMD seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the maintenance period.*

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Seizure frequency (SF) per 28 days during a given period is calculated using only available data during the period as follows:

$$\text{SF per 28 days} = \frac{\text{Number of seizures during period}}{\text{Number of non-missing seizure diary days in period}} \times 28$$

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

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

For calculation of seizure frequency per 28 days, time periods are defined as follows. These periods are only defined for subjects who took at least one dose of study drug.

The **Baseline Period** for the purpose of 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.

The Full **Treatment Period** includes the day of first dose of study drug and all days up to and including the day before visit V11 for subjects who completed that visit. If that visit did not occur, the Full Treatment Period will include all days up to and including the day before the last

study visit or the day of first dose of study drug + 111 days, whichever is earlier. By this definition, the Full Treatment Period may include dose tapering and follow-up days for subjects who prematurely discontinue from the study.

The **Maintenance Period** starts 28 days after the first dose of study drug and includes all days up to and including the last day of the Full Treatment Period. Subjects who discontinue study drug or initiate tapering due to discontinuation during the first 28 days beginning with the day of first dose of study drug do not have a Maintenance Period.

Seizure frequency will be collected via an electronic daily seizure and medication diary. The electronic diary will allow a 7-day window for data entry/correction by the subject/parent or caregiver.

The electronic daily seizure and medication diary is an observer-reported clinical outcome assessment measure that captures seizures noted as occurring as individual seizures and seizures occurring in a cluster. Countable and uncountable seizures occurring within a cluster will be captured. Subject/parent or caregiver will be the observers and reporters in the current study.

All seizure events will be recorded starting at the screening/baseline period up until the follow-up visit.

Only seizure classification/descriptions approved by The Epilepsy Study Consortium (TESC) *will be collected in the electronic daily seizure and medication diary for this study.*

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MMD seizures include the following 8 seizure types noted in the table below, which are among the seizure classifications approved for this study by TESC. For the efficacy analyses by seizure type, any seizure type lasting less than 30 mins will be captured under the specific seizure type (e.g., Hemiclonic or Focal Clonic; Focal to Bilateral Tonic-Clonic; Generalized Tonic-Clonic; Bilateral Clonic; Tonic) rather than under the category of Convulsive Status Epilepticus. Any seizure type lasting 30 minutes or longer will be captured under the category of Convulsive Status Epilepticus which is also included in the MMD definition, as noted below.

Primary Outcome Seizure Types: Major Motor Drop (MMD)	
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., Hypermotor 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

A complete list of seizure classifications approved for this study is provided in Appendix 9.4. Definitions of seizure types are provided in the Study Manual. For each patient, any existing or new seizure types entered in the seizure diary will be adjudicated by the TESC.

For all seizure frequency calculations in this study, the number of seizures on a given day is the sum of the number of countable or repetitive countable seizures, plus a count of 1 for each reported uncountable seizure event. The primary endpoint for this study is based on the number of MMD seizures. Refer to Section 9.2.4 for details of seizure data handling.

6.5.1.2 Main Analytical Approach

The primary efficacy analysis will compare percent change from baseline in frequency of MMD seizure per 28 days during the Full Treatment Period between the soticlestat and placebo groups, based on the mITT analysis set using a rank ANCOVA model. The model will have rank of percent change from baseline in frequency of MMD seizures per 28 days during the Full Treatment Period (Maintenance Period for EMA registration) as the outcome variable and treatment group, stratification age group (≤6 years, >6 years), and rank of baseline seizure frequency per 28 days as predictors. Rank transformation on the outcome and baseline will be done on the combined data from soticlestat and placebo subjects. Tied ranks will be assigned their mean value. The null hypothesis that the coefficient of the treatment group term in the model is 0 will be tested and the p-value will be reported.

The Hodges-Lehmann estimator will be used as the primary estimator of the treatment effect. The resulting estimate will be interpreted as the location shift of percent change from baseline in MMD seizure frequency per 28 days during the Full Treatment Period (Maintenance Period for EMA registration) between the soticlestat and placebo treatment groups. The asymptotic (Moses) 95% confidence interval will be presented.

The method of calculating seizure frequency per 28 days for the primary analysis is described in Section 6.5.1.1. In accordance with the treatment policy strategy for handling intercurrent events, all seizure diary data collected during the Full Treatment Period will be used even if collected after an intercurrent event. For the primary analysis, only available seizure diary data (i.e., non-missing seizure diary days) are used in the calculation of seizure frequency. This approach assumes that the seizure frequency during the missing seizure diary days is equal to the seizure frequency during the non-missing seizure diary days.

The primary analysis for EMA registration will include all subjects in the mITT set who have at least one non-missing seizure diary day during the Maintenance Period. This analysis is based on principal stratum of subjects who would not discontinue study drug or initiate tapering due to discontinuation during the first 28 days regardless of assigned treatment. A principal stratification framework that allows for interpretation of the primary analysis in terms of causal effects is described in Section 6.5.1.3.5, along with a tipping point sensitivity analysis.

Descriptive summaries of MMD seizure frequency per 28 days during the Baseline Period, Full Treatment Period, and Maintenance Period will be provided. Descriptive summaries will also be provided for percent change from baseline in MMD seizure frequency per 28 days during the Full Treatment Period and the Maintenance Period.

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6.5.1.3 Sensitivity Analysis

All sensitivity analyses will evaluate the primary estimand. For brevity, the term "seizure frequency" will indicate "MMD seizure frequency". Sensitivity analyses are performed on the mITT analysis set unless indicated otherwise.

6.5.1.3.1 Sensitivity Analysis Considering Multiple Imputations with a Missing not at Random Mechanism

The Full Treatment Period will be divided into the following periods, and multiple imputations will be implemented based on a pattern mixture modeling approach using a control-based pattern imputation to impute seizure frequency during periods where data is missing, under the assumption that data are missing not at random:

- **Period 1** consists of the first 28 days beginning with the day of first dose of study drug.
- **Period 2** consists of the subsequent 28 days after Period 1.
- **Period 3** consists of the subsequent 28 days after Period 2.
- **Period 4** consists of the subsequent 28 days after Period 3 for subjects who did not complete visit V11. For subjects who completed that visit, the last day of Period 4 is the day before the visit.

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Let $Y_k = \log(1 + \text{seizure frequency per 28 days during the Period } k)$ for $k = 1, 2, 3, 4$. Define Y_B similarly for the Baseline Period. Subjects who have no seizure diary data during Period k will have Y_k missing. Early study discontinuations will induce a monotone missing data pattern on Y_1, Y_2, Y_3, Y_4. It is assumed that after discontinuation, subjects in the soticlestat group will experience a similar rate of MMD seizures as subjects in the placebo group. Sequential monotone regression will be applied using the imputation model where Y_k depends linearly in expectation on $Y_B, Y_1, \ldots, Y_{k-1}$, and age stratum. The imputation model will be fitted to available data from placebo subjects only, and the missing values from both placebo and soticlestat groups will be imputed from the fitted model sequentially by Period until all missing values have been imputed. A total of 100 imputed datasets will be generated via PROC MI in SAS using a pre-specified seed.

In case the missing pattern is not monotone (e.g., a subject has seizure diary data during Periods 2 and 4 but not Period 3), imputation will be applied first to restore data to monotonicity using the MCMC method using PROC MI with IMPUTE=MONOTONE statement. Then monotone regression imputation will be applied once on each dataset, resulting in 100 complete datasets. A seed value of 14823 will be used for multiple imputation analysis.

Each subject's seizure frequency per 28 days during the Full Treatment Period or Maintenance Period is derived from their completed, possibly imputed, data Y_1, Y_2, Y_3, Y_4 as the weighted sum $\sum_k w_k \max\{0, \exp(Y_k) - 1\}$ with k ranging from 1 to 4 for the Full Treatment Period, and from 2 to 4 for the Maintenance Period. The weights are defined as

$$w_k = \frac{\text{Number of non-missing seizure diary days during Period k}}{\text{Number of non-missing seizure diary days during Treatment (or Maintenance) Period}}$$

If Y_k was imputed, the number of non-missing diary seizure days during Period k is set to the number of days in Period k, and this number of days is added to the denominator. Percent change from baseline in seizure frequency per 28 days will subsequently be derived per the formula in Section 6.5.1.1.

For each completed dataset, the rank ANCOVA model will be fitted, and the 100 estimated coefficients of the treatment group term and their standard errors will be combined via Rubin's rule to generate an overall treatment effect estimate and standard error, which in turn will be used to calculate a p-value to test the null hypothesis of no treatment effect. Similarly, the Hodges-Lehmann estimate and asymptotic standard error will be calculated for each completed dataset and combined via Rubin's rule to generate an overall estimate of location shift and standard error. The asymptotic 95% CI will be derived in turn.

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6.5.1.3.2 Sensitivity Analysis with Van Elteren Test

Percent change from baseline in MMD seizure frequency per 28 days during the Full Treatment Period (Maintenance Period for EMA registration) will be compared between treatment groups using the van Elteren test stratified by age stratum. The p-value will be presented. Only subjects who have at least one non-missing seizure diary day during the Maintenance Period will be included in the Maintenance Period analysis.

6.5.1.3.3 Sensitivity Analysis with Wilcoxon Rank Sum Test

Percent change from baseline in MMD seizure frequency per 28 days during the Full Treatment Period (Maintenance Period for EMA registration) will be compared between treatment groups using the Wilcoxon rank sum test. The p-value will be presented. Only subjects who have at least one non-missing seizure diary day during the Maintenance Period will be included in the Maintenance Period analysis.

6.5.1.3.4 Sensitivity Analysis with Sex Added to the Rank ANCOVA Model

The primary analysis as described in Section 6.5.1.2 will be repeated using a rank ANCOVA model with sex included as a factor.

6.5.1.3.5 Sensitivity Analysis on the Principal Stratification Strategy for EMA Registration

If >5% of subjects discontinue study drug or initiate tapering due to discontinuation during the first 28 days beginning with the day of first dose of study drug in either treatment group, a tipping point sensitivity analysis will be performed for EMA registration. A potential outcomes and principle stratification method [2] is provided here to allow interpretation of the primary estimate as a causal effect. Then a procedure for a tipping point sensitivity analysis is described.

Let Y = Percent change from baseline in MMD seizure frequency per 28 days for a subject during maintenance period

Let S = Status indicating whether a subject experienced the intercurrent event of discontinuing drug or initiating tapering due to discontinuation during the first 28 days (D=discontinued drug or initiated tapering during the first 28 days, C=continued drug into maintenance period)

Potential outcomes:

- Y_1 and Y_0 denote potential outcomes for a subject if assigned to soticlestat or placebo, respectively.
- S_1 and S_0 denote the potential intercurrent event status for a subject if assigned to soticlestat or placebo, respectively.

Following the principal stratification approach, let U denote the principal stratum defined by the joint potential status (S_1, S_0) of a subject. There are four principal strata defined by the 4 possible joint values $(S_1, S_0) = CC, DC, CD, DD$.

- "Always continue" ($U = CC$): Participant would always continue drug into maintenance regardless of treatment assignment.
- "Continue with placebo only" ($U = DC$): Participant would continue drug under placebo but not soticlestat.
- "Continue with soticlestat only" ($U = CD$): Participant would continue drug with soticlestat but not placebo.
- "Never continue" ($U = DD$): Participant would never continue drug regardless of treatment assignment.

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The primary estimand for EMA registration is the treatment effect in the principal stratum of subjects who would always continue drug into maintenance regardless of treatment assignment. That is, the primary estimand is the causal effect

$$\theta = E(Y_1 | U = CC) - E(Y_0 | U = CC)$$

Note that if the distributions Y_0 and Y_1 shifts of each other, then the difference in expectation is equal to the location shift, which is the treatment effect summary measure of interest.

The primary analysis will use rank ANCOVA to calculate a p-value and the Hodges-Lehmann estimator along with 95% asymptotic confidence interval to estimate the treatment effect (location shift) using only the observed outcomes from subjects who continued drug into the Maintenance Period. Hence the primary analysis provides an unbiased estimate of the estimand

$$\theta_0 = E(Y_1 \mid S_1 = C) - E(Y_0 \mid S_0 = C)$$

In general θ_0 is not a causal effect and does not equal the target estimand θ. Their difference ("Bias") has an exact expression provided by [4]:

$$\theta - \theta_0 = Bias = \frac{\pi_{DC}}{p_0}\beta_0 - \frac{p_1 - p_0 + \pi_{DC}}{p_1}\beta_1$$

Where

- $p_1 = P(CC, CD)$ = Probability of continuing drug if assigned to soticlestat
- $p_0 = P(CC, DC)$ = Probability of continuing drug if assigned to placebo
- $\pi_{DC} = P(DC)$ = Probability of continuing drug under placebo but not soticlestat
- $\beta_0 = E(Y_0 \mid U = DC) - E(Y_0 \mid U = CC)$ = Difference in average potential outcomes under placebo between the "continue with placebo only" and "always continue" strata.
- $\beta_1 = E(Y_1 \mid U = CD) - E(Y_1 \mid U = CC)$ = Difference in average potential outcomes under soticlestat between the "continue with soticlestat only" and "always continue" strata.

The base case assumption for the primary analysis is $\beta_0 = \beta_1 = 0$; i.e. the placebo effect is the same in the "continue with placebo only" and "always continue" strata, and the soticlestat effect is the same in the "continue with soticlestat only" and "always continue" strata. With this set of base case assumptions, we have $\theta = \theta_0$, and the primary analysis will provide an unbiased estimate of the primary estimand.

A tipping point sensitivity analysis will be performed to evaluate the robustness of the primary estimate. This will be done by varying the sensitivity parameters π_{DC}, β_0, β_1 until the upper bound of the two-sided 95% confidence interval for θ equals 0; i.e. until the results are borderline statistically significant in favor of soticlestat. For the purpose of the tipping point analysis, "statistical significance favoring soticlestat" means that the upper bound of the two-sided 95% CI for the treatment difference is <0.

The parameters p_0 and p_1 will be estimated directly from the data as the proportion of subjects on placebo and soticlestat, respectively, who continue drug into the Maintenance Period. The sensitivity parameters π_{DC}, β_0, and β_1 cannot be estimated directly. It can be shown [3] that π_{DC} is bounded between $\max(0, p_0 - p_1)$ and $\min(p_0, 1 - p_1)$. However, β_0 and β_1 are unrestricted. The tipping point analysis will proceed as follows.

1. The 95% CI for θ will first be calculated from the primary estimate under the base case assumption with Bias=0. Let the $\hat{\theta}_0 - A$ and $\hat{\theta}_0 + A$ be the lower and upper limits of this CI.
2. In general, to calculate the 95% CI for θ when the base case assumption may not hold, i.e., when Bias≠0, the Bias term will be added to the lower and upper bounds of the base case CI to obtain a bias-corrected 95% CI from $\hat{\theta}_0 - A + Bias$ to $\hat{\theta}_0 + A + Bias$.
3. Define a grid of equally spaced values spanning the interval $[\max(0, p_0 - p_1), \min(p_0, 1 - p_1)]$. The default number of grid points will be 4, but more or fewer points may be considered depending on the observed width of the interval.
4. Assign π_{DC} iteratively to each value in the grid. For each value of π_{DC}, let $w_0 = \frac{\pi_{DC}}{p_0}$ and $w_1 = \frac{p_1 - p_0 + \pi_{DC}}{p_1}$, so the equation $\hat{\theta}_0 + A + w_0\beta_0 - w_1\beta_1 = 0$ defines the set of tipping point pairs (β_0, β_1) at which the conclusion changes from favoring soticlestat to not favoring soticlestat. This linear equation will be plotted with β_0 on the horizontal axis and β_1 on the vertical axis. The area representing values (β_0, β_1) for which the

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conclusion does not favor soticlestat (i.e., the region of non-significance $\hat{\theta}_0 + A + w_0\beta_0 - w_1\beta_1 \geq 0$) will be shaded.

5. Clinical plausibility of parameter values (β_0, β_1) in the region of non-significance will be discussed.

6.5.1.3.6 Sensitivity Analysis on the Use of J-tube

A sensitivity analysis may be performed to evaluate the impact of J-tube use when appropriate.

6.5.1.3.7 Sensitivity Analysis to Exclude Subjects from Ukraine

A sensitivity analysis to explore the potential impact of the Russia-Ukraine crisis may be performed. The main analytical approach described in Section 6.5.1.2 would be used with subjects from Ukraine excluded from the analysis. Results will be reported for both the Full Treatment Period and the Maintenance Period.

6.5.1.4 Supplementary Analyses

Not applicable.

6.5.1.5 Additional Analyses

The percent change from baseline in frequency of MMD seizure per 28 days will be summarized by treatment group every 4 weeks using the time intervals Period 1 (weeks 1-4), Period 2 (weeks 5-8), Period 3 (weeks 9-12), and Period 4 (weeks 13-16/V11) as defined in Section 6.5.1.3.1, based on the mITT analysis set. The Hodges-Lehmann estimator of location shift of percent change from baseline in MMD seizure frequency per 28 days will be used as the primary estimator of the treatment effect in each of the 4 periods. The asymptotic (Moses) 95% confidence interval will be presented.

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6.5.2 Analysis of Secondary Endpoints Tested in the Gatekeeping Procedure

6.5.2.1 Secondary Endpoint Analysis: Proportion of Responders

6.5.2.1.1 Derivation of Endpoint

Subjects with ≥50% reduction from baseline in MMD seizure frequency per 28 days during the Full Treatment Period are considered responders.

For EMA registration:

Subjects with ≥50% reduction from baseline in MMD seizure frequency per 28 days during the Maintenance Period are considered responders.

The method of calculating percent change from baseline in MMD seizure frequency per 28 days is explained in Section 6.5.1.1.

6.5.2.1.2 Main Analytical Approach

The Cochran-Mantel-Haenszel (CMH) test stratified by age stratum (≤6 years, >6 years) will be used to compare the proportion of responders during the Full Treatment Period in the soticlestat vs placebo groups.

For EMA registration:

The proportion of responders during the Maintenance Period will be compared between treatment groups using the CMH test stratified by age stratum. This analysis will include all subjects in the mITT analysis set who have at least one non-missing seizure diary day during the Maintenance Period.

The Mantel-Haenszel estimator of the common odds ratio will be presented along with 95% CIs based on the Robins, Breslow, and Greenland variance estimate, using the SAS PROC FREQ.

Descriptive statistics for proportions of responders will also be presented by treatment group.

6.5.2.1.3 Sensitivity Analysis

A sensitivity analysis to evaluate the impact of missing data will be performed using multiple imputations following the same control-based pattern imputation approach used for sensitivity analysis of the primary endpoint, as described in Section 6.5.1.3.1.

After 100 completed datasets have been generated and percent change from baseline in MMD seizure frequency per 28 days during the Full Treatment Period and the Maintenance Period has been calculated for each dataset, the responder status (≥50% reduction) for each subject will be derived in each dataset, then the CMH test will be performed on each dataset separately for the Full Treatment Period and for the Maintenance Period. The Mantel-Haenzel estimator of the common odds ratio and the Robins, Breslow, and Greenland variance estimate of the log odds ratio will also be calculated, using the FREQ procedure in SAS.

The estimated log odds ratios and corresponding standard errors will be combined via Rubin's rule and the pooled estimate and standard error will be calculated. An asymptotic 95% CI for the log odds ratio will be derived from the pooled estimates. The estimated odds ratio and 95% CI derived by anti-log transformation will be presented.

The chi-squared statistics from the CMH tests of the 100 datasets will be combined via the chi squared pooling method described in [1] (see also [5]), and the corresponding p-value derived from the pooled statistic will be reported.

Results will be reported for both the Full Treatment Period and the Maintenance Period.

6.5.2.2 Secondary Endpoint Analysis: Care GI-I

6.5.2.2.1 Derivation of Endpoint

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 subject will be rated as follows: 1 (very

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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 V8 and visit V11/ET. At the baseline visit, with input from the parent/caregiver, the investigator or designee documents a description of the participant's overall condition over the past month with respect to seizure control as well as non-seizure symptoms and behavior. The Care GI-I scale is then completed by the caregiver at designated post baseline visits while referencing the baseline description.

6.5.2.2.2 Main Analytical Approach

The main analysis of Care GI-I will compare the ordinal responses at the end of the Full Treatment Period between the soticlestat and placebo groups. For the purpose of Care GI-I analysis and other caregiver or clinician reported scales, the end of the Full Treatment Period is defined as visit V11. If that visit did not occur for a subject, then a last-observation carried forward (LOCF) approach will be used to impute the subject's score.

Let Y be the response at the end of the Full Treatment Period. The following cumulative logit model will be used for analysis:

$$logit\big(P(Y \leq j|\, TRT, AGEGP)\big) = \alpha_j + \beta_1 TRT + \beta_2 AGEGP,\ \ j = 1, \ldots, 6$$

Set TRT=0 for the placebo group and TRT=1 for the soticlestat group, and set AGEGP=0 for subjects ≤6 years old and AGEGP=1 for subjects >6 years old. The null hypothesis that $\beta_1 = 0$ will be tested. The anti-log transform of the treatment effect estimate $\hat{\beta}_1$ and corresponding 95% CI will be reported. The transformed value $exp(\hat{\beta}_1)$ will be interpreted as the odds ratio of obtaining a response in category j or better in the soticlestat group vs placebo group.

The proportion of responses in each category will be summarized by treatment group and by study visit.

A window approach (see Table 6.a) will be used to define the timepoints included in the summary. Refer to Section 9.2.3 for rules to select a record from analysis visit windows.

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Table 6.a Analysis Windows for Care GI-I Summary

Analysis Visit	Analysis Visit Window
V8	The day after the initial dose – the midpoint between the V8 and V11 per protocol (inclusive)
V11	• For subjects who rolled over to the OLE study and OLE V1 date is available, the window is: the midpoint between V8 and V11 per protocol (not inclusive) – V1 of OLE study (inclusive). • For subjects who rolled over to the OLE study and OLE V1 date is not available, the window is: midpoint between V8 and V11 per protocol (not inclusive) –

Table 6.a Analysis Windows for Care GI-I Summary

Analysis Visit	Analysis Visit Window
	min(V11, last scheduled visit including ET if available) (inclusive). • For subjects who did not roll over to the OLE study, the window is: > the midpoint between V8 and V11 per protocol.

6.5.2.2.3 Sensitivity Analysis

A sensitivity analysis will be performed using the van Elteren test, stratified by age stratum. This nonparametric approach does not make assumptions about proportional odds. This analysis will use the same population (with LOCF) as the main analytical approach (Section 6.5.2.2.2).

An additional sensitivity analysis will be performed based on responses for completers only, i.e., subjects who were assessed at visit V11. This analysis will be performed using the same cumulative logit model as the main analysis. The estimated odds ratio, 95% CI, and p-value for the test of no treatment effect will be reported. Descriptive summaries of responses by treatment group and visit will also be provided.

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6.5.2.2.4 Sensitivity Analysis Using Multiple Imputation

A sensitivity analysis will be conducted using multiple imputation under the assumption of a missing not at random (MNAR) mechanism, as an alternative to the last-observation-carried-forward (LOCF) method in the main analytic approach, for imputing missing visit V11 scores. The imputation model for visit V11 scores (visit V8) will include visit V8 (visit V11), treatment group (placebo or soticlestat), and age stratum (≤6 or >6 years old) as covariates. The fully conditional specification (FCS) method will be applied using cumulative logit models for both visits V8 and V11. For missing assessments due to confirmed early discontinuation for any reason or death, a control-based pattern multiple imputation will be used, operating under the assumption that responses in the soticlestat group would mirror those in the placebo group post-discontinuation. For missing assessments due to all other reasons, imputation will be based on the subject's randomized treatment arm.

The imputation process will proceed sequentially, beginning with the imputation of missing data from analysis visit 8, followed by analysis visit 11. A total of 100 imputed datasets will be generated using PROC MI in SAS, with a fixed seed of 35980 to ensure reproducibility. For each imputed dataset, the analysis will employ the same cumulative logit model used in the main analysis. This model estimates the log odds ratio $\hat{\beta}_1$ and its standard error for the treatment effect. The results from these 100 imputed datasets will be aggregated using Rubin's rules to derive an overall estimate of the treatment effect and its standard error. This will then be used to calculate a p-value for the test of no treatment effect. Furthermore, the exponentiated form of the overall treatment effect (odds ratio) and its 95% confidence interval will be reported.

6.5.2.2.5 Supplementary Analysis

A supplementary analysis of Care GI-I will be done to compare the combined responses improvement (scores 1, 2 and 3) versus no change or worse (scores 4, 5, 6, and 7) at the end of the Full Treatment Period between the soticlestat and placebo groups.

The combined responses of Care GI-I at visit V11 will be analyzed using a Cochran-Mantel-Haenszel (CMH) test, stratified by age stratum. If V11 did not occur for a subject, then an LOCF approach will be used to impute the subject's combined response. The Mantel-Haenszel estimator of the common odds ratio will be presented along with 95% CIs based on the Robins, Breslow, and Greenland variance estimate, using the SAS procedure FREQ.

The number and percentage of patients with the combined responses of improvement and no change or worse will be summarized by treatment group and visit.

6.5.2.3 Secondary Endpoint Analysis: CGI-I

6.5.2.3.1 Derivation of Endpoint

The CGI-I (Clinician) is a 7-point Likert scale that the investigator uses to rate a subject's change (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 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 at visit V8 and visit V11/ET. The baseline visit for this assessment occurs on visit V2. At the baseline visit, with input from the parent/caregiver, the investigator or designee documents a description of the participant's overall condition over the past month with respect to seizure control as well as non-seizure symptoms and behavior. The CGI-I scale is then completed by the investigator at designated post baseline visits while referencing the baseline description.

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6.5.2.3.2 Main Analytical Approach

The main analysis of CGI-I will compare the ordinal responses at the end of the Full Treatment Period between the soticlestat and placebo groups. The analysis and data summaries will follow the same approach as for the Care GI-I analysis, per Section 6.5.2.2.2.

6.5.2.3.3 Sensitivity Analysis

The sensitivity analyses described for Care GI-I in Section 6.5.2.2.3 and Section 6.5.2.2.4 will be repeated for CGI-I.

6.5.2.3.4 Supplementary Analysis

Similar supplementary analysis as described for Care GI-I (Section 6.5.2.2.5) will be repeated for CGI-I. For CGI-I, the combined responses will be defined as improvement (scores 1, 2 and 3) and no change or worse (scores 4, 5, 6 and 7).

6.5.2.4 Secondary Endpoint Analysis: CGI-I Nonseizure Symptoms

6.5.2.4.1 Derivation of Endpoint

The CGI-I nonseizure symptoms instrument is a series of single-item assessments that the investigator uses to rate improvement in the 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). At baseline, a symptoms form is completed by the clinician in collaboration with the primary caregiver to assess the subject's status based on the presence of any nonseizure symptoms. The baseline form is intended to serve as a reference for the investigator and caregiver during subsequent visits when assessing change in the subject's condition pertaining to these symptoms.

The investigator or designee will complete the CGI-I Nonseizure Symptoms instrument in consultation with the primary caregiver at visit V8 and visit V11/ET. The baseline visit for this assessment occurs on visit V2.

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6.5.2.4.2 Main Analytical Approach

The main analysis of CGI-I Non-Seizure Symptoms will compare the ordinal responses at the end of the Full Treatment Period between the soticlestat and placebo groups. The analysis will be done separately in each of the three domains: alertness, communication and disruptive behaviors (the testing order will be: alertness, communication, and disruptive behaviors). The analysis and data summaries for each domain will follow the same approach as for the Care GI-I analysis, per Section 6.5.2.2.2.

6.5.2.4.3 Sensitivity Analysis

The sensitivity analyses described for Care GI-I in Section 6.5.2.2.3 will be repeated for each of the three domains in CGI-I Non-Seizure Symptoms.

6.5.2.4.4 Supplementary Analysis

Similar supplementary analysis as those described for Care GI-I in Section 6.5.2.2.5 will be done for each of the three domains in CGI-I Non-Seizure Symptoms. For each domain, the combined responses will be defined as improvement (scores 1, 2 and 3) and no change or worse (scores 4, 5, 6 and 7).

6.5.2.5 Secondary Endpoint Analysis: Change in QI-Disability Score

6.5.2.5.1 Derivation of Endpoint

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. The parent/caregiver-reported questionnaires will be administered at visits V2 (Baseline), V8, and V11/ET *in countries where the questionnaires have been translated into the native language of the region and linguistically validated.*

Each QI-Disability item is rated on a Likert scale of: Never, Rarely, Sometimes, Often, and Very Often. Responses in the negative emotions 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. See Appendix 9.5.1 for the grouping of items into domains. 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.

6.5.2.5.2 Main Analytical Approach

The main analysis of QI-Disability will compare the change from baseline to the end of the Full Treatment Period between the soticlestat and placebo groups. A windowing approach will be used to define analysis timepoints. For this purpose, Analysis Day 1 is defined as the date of first dose. A mixed model for repeated measures (MMRM) will be fitted under a missing at random assumption, with change from baseline as the outcome and baseline score as a fixed continuous effect, and treatment group, age stratum, Analysis Visit, and Analysis Visit by treatment group interaction as fixed categorical effects. An unstructured covariance model will be used. If there are convergence issues, an AR(1) autoregressive model will be used. If there are convergence issues with the AR(1) model, other covariance structures will be considered, as appropriate. A test of the contrast between soticlestat and placebo groups and at Analysis V11 will be the primary basis for inference. The model estimated means by treatment group and difference in means between treatment groups at each Analysis Visit will be provided along with 95% CIs. In addition, observed descriptive statistics at Baseline and Analysis Visits will be provided by treatment group.

A window approach (see Table 6.b) will be used to define the timepoints included in the summary. Refer to Section 9.2.3 for rules to select a record from analysis visit windows.

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Table 6.b Analysis Windows for QI-Disability

Analysis Visit	Analysis Visit Window
V8	Day after first dose day - Day before Analysis Day 57 (inclusive)
V11	• For subjects who rolled over to the OLE study, if V1 date of OLE is available, the window is: Analysis Day 57 (inclusive) – V1 of OLE study (inclusive). If V1 date of OLE is not available, use min(V11, last scheduled visit including ET if available) (inclusive) as upper the bound. • For subjects who did not roll over to the OLE study, the window is: ≥Analysis Day 57.

6.5.2.6 Secondary Endpoint Analysis: CGI-I Seizure Intensity and Duration

6.5.2.6.1 Derivation of Endpoint

The CGI-I Seizure Intensity and Duration instrument is used by the parent/caregiver to rate changes in intensity and duration of MMD seizures from the first assessment. 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 at visit V8 and visit V11/ET. The baseline visit for this assessment occurs on visit V2. At the baseline visit, with input from the parent/caregiver, the investigator or designee documents the caregiver's description of the intensity and/or duration of the participant's most impactful seizures over the past month (excluding status epilepticus). The CGI-I Seizure Intensity and Duration scale is then completed by the parent/caregiver at designated post baseline visits while referencing the baseline description.

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6.5.2.6.2 Main Analytical Approach

The main analysis of CGI-I Seizure Intensity and Duration will compare the ordinal responses at the end of the Full Treatment Period between the soticlestat and placebo groups. The analysis and data summaries will follow the same approach as for the Care GI-I analysis, per Section 6.5.2.2.2.

6.5.2.6.3 Sensitivity Analysis

The sensitivity analyses described for Care GI-I in Section 6.5.2.2.3 will be repeated for CGI-I Seizure Intensity and Duration.

6.5.2.6.4 Supplementary Analysis

Similar supplementary analysis as those described for Care GI-I (Section 6.5.2.2.5) will be done for CGI-I Seizure Intensity and Duration. For CGI-I Seizure Intensity and Duration, the combined responses will be defined as improvement (scores 1, 2 and 3) and no change or worse (scores 4, 5, 6 and 7).

6.5.3 Other Secondary Endpoints Analysis

6.5.3.1 Percent Change from Baseline in Frequency for all Seizures per 28 Days

Percent change from baseline in frequency per 28 days of all seizures during the Full Treatment Period and Maintenance Period will be analyzed using the main analytic approach for the primary efficacy analysis per Section 6.5.1.2. Per the main analytic approach, Hodges-Lehmann estimators and 95% CIs will be reported. P-values and summary statistics by treatment group will be reported for descriptive purposes.

6.5.3.2 Responder Analysis

The number and proportion of subjects with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, and >75% to ≤100% reduction from the baseline in MMD seizure frequency per 28 days during the Full Treatment Period will be summarized by treatment group. Seizure frequency reduction of >X% is equivalent to percent change from baseline in seizure frequency of < -X%. A cumulative response curve will be plotted showing the proportion of subjects with >X% reduction from baseline in MMD seizure frequency per 28 days as a function of X, with separate curves for each treatment group.

For EMA registration, the same analysis will be done for the Maintenance Period.

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6.5.3.3 Change from Baseline in Proportion of MMD Seizure-Free Days

The proportion of MMD seizure-free days during a period is defined as the number of non-missing seizure diary days when no MMD seizures occurred during the period divided by the number of non-missing seizure diary days during the period. The proportion of MMD seizure-free days will be summarized descriptively for the Baseline Period and Full Treatment Period by treatment group. The change from baseline in proportion of MMD seizure-free days, defined as the proportion of seizure-free days during the Full Treatment Period minus the proportion of seizure-free days during the Baseline Period, will be summarized descriptively by treatment group. The treatment effect on change from baseline in proportion of MMD seizure-free days will be estimated using a linear model with treatment group and age stratum as factors and baseline proportion as a covariate. The estimated main effect of treatment group, interpreted as the adjusted difference in group means, will be reported along with 95% CI.

6.5.3.4 Longest MMD Seizure-free Interval

The longest MMD seizure-free interval is defined as the longest consecutive number of days during the Full Treatment Period on which there were no MMD seizures.

If a subject has one or more consecutive days of missing seizure diary data, the first day of missing seizure diary data will be considered as MMD seizure-free provided it is preceded by an MMD seizure-free day, and all other subsequent days, starting from the second day with missing seizure data, will be assumed to have MMD seizure occurrence, until the next non-missing seizure data are available. Identification of seizure free days will be based on the rules described in Section 9.2.4.

The longest MMD seizure-free interval will be summarized descriptively by treatment group. The treatment effect on the longest MMD seizure-free intervals will be estimated using a linear model with treatment group and age stratum as factors. The estimated main effect of treatment group, interpreted as the adjusted difference in group means, will be reported along with 95% CI.

6.5.3.5 Number of 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 Full Treatment Period when rescue ASM is used can be derived, where Full Treatment Period is as defined in Section 6.5.1.1. The proportion of days during the Full Treatment Period will also be calculated, using the number of days during the Full Treatment Period as the denominator. The number of days when rescue ASM is used will be summarized descriptively. The treatment effect on the proportion of days when rescue ASM is used will be estimated using a linear model with treatment group and age stratum as factors. The estimated main effect of treatment group, interpreted as the adjusted difference in group means, will be reported along with 95% CI.

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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 Full Treatment Period. 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 Full Treatment Period. Analyses will be based on the data available in EDC.

6.5.4 Exploratory Endpoints Analysis

6.5.4.1 Percent Change from Baseline in Frequency per 28 Days of Each Seizure Type Identified at the Time of Screening or Baseline

Percent change from baseline in frequency per 28 days of each seizure type during the Full Treatment Period will be compared between soticlestat and placebo groups using the main analytic approach for the primary efficacy analysis per Section 6.5.1.2. The list of seizure types collected in the daily diary is provided in Appendix 9.4. For each seizure type, only subjects who experience at least 1 seizure of that type during the baseline period (as defined in Section 6.5.1.1) will be included in the analysis. Per the main analytic approach, Hodges-Lehmann estimators and 95% CIs will be reported. P-values and summary statistics by treatment group will be

reported for descriptive purposes. Note that seizure types O (Infantile Spasms [Under 3 Years of Age]) and P (Epileptic Spasms [3 Years of Age and Older]) will be grouped into single type in the summary outputs.

6.5.4.2 Change in EQ-5D-5L and Visual Analogue Scale (EQ-VAS) Scores

The EQ-5D-5L is the 5–response level version of the EQ-5D instrument. It consists of 2 sections, a descriptive system questionnaire and the EQ visual analogue scale (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 ticking the box next to the most appropriate statement in each of the dimensions. In addition, the EQ-VAS is used to indicate the general health status, with 100 indicating the best health status. These questionnaires will be administered at baseline and at visit V11/ET.

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 presenting the number 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 to assess change from baseline to V11/ET. EQ-VAS scores will be summarized descriptively by visit and treatment group. Change in EQ-VAS from baseline to post-baseline will be summarized descriptively by treatment group. A higher EQ-VAS score implies a better outcome.

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The change from baseline on the EQ-VAS score will be analyzed using an ANCOVA with baseline as a covariate, treatment and age stratum as fixed factors. The analysis will be performed using observed cases only. Only assessments pertaining to the caregivers' own health quality of life will be included in the analysis.

A window approach (see Table 6.c) will be used to define the timepoints included in the summary. Refer to Section 9.2.3 for rules to select a record from analysis visit windows.

Table 6.c Analysis Windows for EQ-5D-5L

Analysis Visit	Analysis Visit Window
V11	• For subjects who rolled over to the OLE study, the window is: Day after first dose day (inclusive) – V1 of OLE (inclusive) study if V1 date of OLE is available. If V1 date of OLE is not available, the upper bound is min(V11, last scheduled visit including ET if available) (inclusive) • For subjects who did not roll over to the OLE study, the window is: ≥ Day after first dose day

6.5.5 Subgroup Analyses

The main analytic approach for the primary analysis will be conducted for the following subgroups:

- Age stratum subgroups (subjects of age ≤6 years; subjects of age >6 years) with the modification of not including age stratum as a predictor in the rank ANCOVA model.

6.5.6 Additional Exploratory Analyses

Analyses may be performed to explore efficacy endpoints in these subpopulations:

- Pediatric subjects (<18 years old) and adult subjects (18 years or older)
- Subgroups based on disease etiology or history, specifically:
  - Structural. This subgroup includes subjects for whom any of the following were reported as definite or possible etiologies: intraventricular hemorrhage; malformations of cortical or other brain development with or without known genetic determinants; mesial temporal sclerosis; neoplasia; neurocutaneous syndromes; stroke; traumatic brain injury.
  - Genetic. This subgroup includes subjects for whom any of the following were reported as definite or possible etiologies: genetic and chromosomal development encephalopathies; genetic or presumed genetic.
  - Unknown. This subgroup includes subjects for whom any of the following were reported as definite or possible etiologies: developmental encephalopathy of unknown cause; epilepsy of unknown cause.
  - History of infantile spasms. This subgroup includes subjects for whom infantile spasms was reported on medical history.
- Subgroups defined according to the number of prior or baseline ASMs.
- Subjects who took rescue medication during the treatment period and subjects who did not take rescue medications during the treatment period.
- Subgroups defined according to whether any CYP3A4 inducers were used as concomitant ASMs. CYP3A4 inducers include carbamazepine, phenobarbital, phenytoin, and primidone.

Analyses may be performed to explore efficacy endpoints under the following alternative definitions of drop seizures (refer to Section 9.4 for a complete list of seizure classifications collected in the daily diary):

- Alternative definition 1: Drop seizures as defined by seizures of these types:
  - Generalized Tonic-Clonic
  - Tonic Seizures Involving Major Body Areas such as Lower Extremities or Trunk Leading to Fall or Likely Fall
  - Tonic Seizures Without Fall or Without Likely Fall (e.g., Head Drop or Upper Extremities Only)
  - Atonic Seizures Involving Major Body Areas such as Lower Extremities or Trunk Leading to Fall or Likely Fall

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  - Atonic Seizures Without Fall or Without Likely Fall (e.g., Head Drop or Upper Extremities Only)
- Alternative definition 2: Drop seizures as defined by the seizures of these types:
  - Focal to Bilateral Tonic-Clonic
  - Generalized Tonic-Clonic
  - Tonic Seizures Involving Major Body Areas such as Lower Extremities or Trunk Leading to Fall or Likely Fall
  - Tonic Seizures Without Fall or Without Likely Fall (e.g., Head Drop or Upper Extremities Only)

6.6 Safety Analysis

Descriptive statistics will be used to summarize all safety endpoints for each of the treatment groups and overall*. AEs will be summarized using the safety analysis set. All AEs will be coded using MedDRA. Data will be summarized using Preferred Terms and primary System Organ Classes.*

Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight, and ECG parameters as appropriate.

All data will be listed.

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6.6.1 Adverse Events

In this study, Adverse Event (AE) *refers to both* pretreatment events (PTEs) and treatment-emergent adverse events (TEAEs)*. PTEs are AEs that started after the signing of informed consent but before receiving any study drug.*

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has been administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

An SAE is defined as any untoward medical occurrence that at any dose:

1. *Results in DEATH.*
2. *Is LIFE THREATENING.*
   - *The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.*
3. *Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.*
4. *Results in persistent or significant DISABILITY/INCAPACITY.*

5. *Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.*
6. *Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:*
    - *May require intervention to prevent items 1 through 5 above.*
    - *May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.*

A TEAE is defined as any AE that starts or increases in severity during or after the first dose of study drug of this study and prior to the first dose of study drug of the OLE for subjects rolling over to the OLE, or through the last study visit for subjects not rolling over to the 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.

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).

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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.

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 severity or relatedness summaries, if a subject reports multiple AEs coded to the same SOC or PT, the AE with maximum severity or strongest relationship will be included in the summary.

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

In general, AEs will be tabulated by treatment group and overall. The tables will include the number and percentage (N[%]) of subjects. Summary tables that will be generated will include, but may not be limited to:

- Overall TEAEs
- TEAEs by SOC and PT
- Frequently occurring ($\geqslant$ 5% of subjects in either one of the treatment groups) TEAEs by PT: the 5% cut-off value will be applied before rounding
- TEAEs by Maximum Severity, SOC and PT
- Drug-Related TEAEs by SOC and PT
- TEAEs leading to Study Drug 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 PTEs, TEAEs, TEAEs leading to study drug discontinuation, SAEs, and TEAEs that resulted in death.

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6.6.2 Adverse Events of Special Interest

This study has 3 types of AEs of special interest, as described in detail in the protocol.

- *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 TEAEs of special interest and number of subjects will be tabulated by treatment group and overall. Each type of adverse event of special interests will be listed.

6.6.3 Other Safety Analysis

6.6.3.1 Clinical Laboratory Evaluations

Clinical laboratory tests will be assessed using the Safety Analysis Set and will be evaluated and presented using International System of Units (SI) units unless otherwise stated. Refer to

Protocol Section 9.1.11.3 as well as the schedule of the events for a list of all clinical laboratory tests.

All laboratory test parameters will be displayed in individual subject data listings in SI units. 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.

No inferential statistics will be presented unless otherwise stated.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed and change from baseline values will be presented for quantitative data. 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, and lab results below or equal to lower limit of quantification (LLOQ) will be set to LLOQ/2; lab results above or equal to upper limit of quantification (ULOQ) will be set to ULOQ. For details, refer to Section 9.2.3.

A window approach (see Table 6.d) will be used to define the timepoints included in the summary. Refer to Section 9.2.3 for rules to select a record from analysis visit windows.

Shift tables for qualitative parameters of Hematology and Chemistry will be created. For shift tables, both central and local lab data will be used. For details, refer to Section 9.2.3. The same window approach (Table 6.d) will be used.

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Table 6.d Analysis Windows for Laboratory Evaluations Summary

Analysis Visit	Analysis Visit Window
V9	The next day after the day of the initial dose – the midpoint between V9 and V11 per the protocol schedule (inclusive)
V11	> the midpoint between V9 and V11 as per the protocol schedule. For subjects who rolled over to the OLE study, the upper bound of the window is the date of V1 of the OLE (inclusive) if available, and if V1 of OLE date is not available it is min(V11, last scheduled visit including ET if available) (inclusive).

For urinalysis, qualitative parameters will be summarized by treatment group and overall, in shift tables (as applicable) comparing the results at each scheduled post-baseline visit with those at the baseline visit. The aforementioned window approach specified in Table 6.d will be used.

For laboratory parameters with normal reference ranges, the number and percentage of subjects with at least one postbaseline measurement outside of the normal reference range will be summarized by treatment group and overall.

Listings of all clinical safety laboratory data will be provided in SI units. Laboratory data outside of the normal reference range will be indicated in the listings. For laboratory data ≤LLOQ or ≥ULOQ, original data will be presented in the listing and will be flagged. The listing will include site number, subject identifier, age, gender, treatment group, study visit, and sample collection date.

Refer to Section 9.2.3 for rules to select a record from analysis visit windows.

6.6.3.2 Vital Signs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize vital sign parameters (including height, weight, 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. A window approach (Table 6.d) as described in Section 6.6.3.1 will be used. Refer to Section 9.2.3 for rules to select a record from analysis visit windows.

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.

6.6.3.3 12-Lead ECG

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters will be presented for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. A window approach (Table 6.d) as described in Section 6.6.3.1 will be used. Refer to Section 9.2.3 for rules to select a record from analysis visit windows. No inferential statistics will be presented.

Overall ECG interpretation category (normal, abnormal not clinically significant, abnormal clinically significant) is collected at V1, V2, V9 and V11. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal limits, abnormal not clinically significant, abnormal clinically significant, and not evaluable interpretations with missing, if applicable, and total categories by treatment group. The worst interpretation within the window will be used for the shift table.

For each treatment group, the number and percentage of subjects with worst post-baseline QTcF in each of these categories will be presented: <450 msec, 450 msec – <480 msec, 480 msec – 500 msec, >500 msec, and Missing. In addition, the number and percentage of subjects with worst QTcF change from baseline in each of these categories will be presented: <30 msec, 30 msec – 60 msec, > 60 msec, and Missing. A higher QTcF value implies a worse outcome.

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.

6.6.3.4 C-SSRS

Suicidal ideation and behavior will be assessed in children aged ≥6 years by use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, subject endorses thoughts

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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).

Two versions of the C-SSRS will be used in this study for all participants ages 6 through 21 years: the C-SSRS Children's Screening/Baseline (recall period lifetime/12 months) and the C-SSRS Children's Since-Last-Visit.

C-SSRS analysis will be based on subjects in the safety analysis set who have at least 1 post-baseline C-SSRS measurement, regardless of whether they had a baseline C-SSRS measurement.

For each C-SSRS question, the baseline will be the worst measurement (including life-time measurement) prior to initial dose of study drug. For details, refer to Section 9.2.2. For post-baseline assessments, the same window approach described in Section 6.6.3.1 will be used as per Table 6.d.

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.e will be used to determine the C-SSRS category of a subject.

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Table 6.e Severity Rank for C-SSRS Questions

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

The number and percentage of subjects with suicidal ideation, suicidal behavior, and the number and percentage of subjects who have "Yes" answers of the suicidal ideation and behavior questions will be summarized by treatment group for each post-baseline visit, using the same

windows as described in Table 6.d. The baseline values (per Section 9.2.2) will also be included in the summary.

Shifts in C-SSRS will be presented as cross-tabulation (baseline versus worst post-baseline categories as in Table 6.e) of numbers and percentages of subjects of no suicidal ideation or suicidal behavior or non-suicidal self-injurious behavior, non-suicidal self-injurious behavior, suicidal ideation, suicidal behavior, and missing by treatment group.

C-SSRS data will also be listed.

6.6.3.5 Ophthalmological Evaluations

Ophthalmological evaluations will be done at V1 and V11/ET, while the examination at V11 is applicable only for subjects who complete the 16 weeks of double-blind treatment (not applicable for ET subjects) and may be conducted within a 14-day window before V11.

The data of the following items will be summarized in terms of number and percentage of subjects in each of ophthalmological evaluations category by left eye, right eye, both eyes and either eye:

- Visual Acuity:
  - V11: Has the visual acuity of the right/left eye significantly declined since the last visit?
- Cataract Screening:
  - Baseline and V11: Are there any anterior or posterior lens opacities in the right/left eye?
  - V11: Has the opacity in the right/left eye worsened since the last visit?
- Fundoscopic Examination:
  - Baseline and V11: Right/left Eye Optic Nerve Exam Interpretation
  - Baseline and V11: Right/left Eye Retinal Exam Interpretation

The analysis visit window of V11 is defined below.

- For subjects who did not roll over to OLE study window will be ≥ Day after first dose
- For subjects who rolled over to the OLE study, the window is:
  - Day after first dose day – V1 date of OLE study if that date is available (inclusive)
  - If OLE V1 date is not available, Day after first dose day – min(V11, last scheduled visit including ET if available) (inclusive)

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For the above summaries, if multiple post-baseline measurements are available, the latest post-baseline measurement will be mapped to V11. If multiple measurements are recorded at the same time, then the worst measurement will be used.

6.6.3.6 Physical Examination

Physical examination data will be listed.

6.6.3.7 New Seizure Types

The number and percentage of patients who develop new seizure types post-study treatment initiation will be summarized for each new seizure type and all new seizure types by treatment group and overall. The data will also be listed.

6.6.4 Extent of Exposure and Compliance

Subject compliance with study drug will be assessed at each visit.

Subjects who are significantly noncompliant will be discontinued from the study. A subject will be considered significantly noncompliant if he or she missed more than 20% of study medication during the study duration unless there is a valid reason for interruption in the study medication such as hospitalization.

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Duration of exposure to double-blind study medication is defined as (date of last dose – date of first dose +1). Total dose is defined as the sum of actual doses (all non-missed doses are considered full dose).

Total dose taken, average daily dose, and duration of exposure (days) will be summarized for all patients by stratum, treatment and overall based on the safety analysis set. In addition, the number and percentage of subjects in each maintenance dose categories (< dose 1, dose 1, dose 1 - dose 2, dose 2, dose 2 – dose 3, dose 3 and > dose 3 as per Table 2.a – Table 2.d) will be summarized. 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.

Study medication data will be collected by the case report form. The number of tablets returned will be collected also.

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

1. Using the exposure data captured by case report form, as [(dose recorded as taken) / (total planned dose)]x 100%,
2. Using number of returned tablets, [(dose dispensed – dose returned) / (total planned dose)] x 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 <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 (n, mean, SD, median, minimum, and maximum) for each treatment group and overall.

The number and percentage of patients who are significantly non-compliant (compliance < 80%) or not will be summarized.

All study drug administration and compliance data will be listed.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Pharmacokinetic analyses are based on the PK analysis set.

6.7.1.1 Plasma Concentrations of Soticlestat and the Soticlestat Metabolite(s) at Multiple Time Points

Individual plasma concentration-time data for soticlestat and the soticlestat metabolite(s) will be presented in listings and summarized descriptively per nominal visit, geometric mean and geometric coefficient of variation will be reported. 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.

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6.7.1.2 Population Soticlestat PK Modeling Based on Sparse PK

The population PK/PD model developed for soticlestat based on the data from phase 1 studies in healthy subjects and phase 2 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/PD modeling will be reported separately. Available ASM information will be included in the population PK/PD analysis, if appropriate.

6.7.2 Pharmacodynamic Analysis

Pharmacodynamic Analyses are based on the PD analysis set.

6.7.2.1 Percent Change from Baseline in Plasma 24HC

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 quantification (LLOQ) are set to 0 for computing descriptive statistics. Mean percent change from baseline in 24HC over time may be presented graphically.

6.7.2.2 Soticlestat Exposure-PD (Plasma 24HC Level) and Efficacy Response Analysis.

Correlation between change in PD (24HC) and efficacy (change in MMD seizure frequency over the full treatment period) will be investigated. A scatter plot of 24HC percent change from baseline at visit V11/ET vs percent change from baseline in MMD seizure frequency per 28 days will be presented, and Spearman correlation will be calculated.

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

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

6.8.1 Health Care Utilization Analysis

Health care resource utilization including but not limited to emergency room visits and hospitalizations will be summarized and presented in listings.

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6.9 Interim Analysis

The protocol states that a blinded interim analysis may be performed. However, per sponsor's decision, no interim analysis was or is planned to be conducted.

6.10 Data Monitoring Committee

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

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

NA

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
3.1 [Row 5 (Secondary #4) in Table 3.a]	NA	Added content: Testing (sequential) order will be as follows: alertness, communication, and disruptive behaviors. Statistical significance of individual domains within the hierarchy can be asserted with global type 1 error control provided all preceding tests are significant, but statistical significance of the full endpoint consisting of all 3 domains of CGI-I Nonseizure Symptoms, can only be asserted if all 3 domains are statistically significant.	Added details for clarification on testing order (as described already in Table 1.b [Secondary #4]) and related inference.
5.2	All randomized 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.	Updated content: All randomized 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.	Added "for seizures" to align with protocol amendment 2.

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Table 9.a Summary of changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.1	NA	Added content: If a subject is assigned to the wrong age stratum during randomization, the actual age, collected as a part of demographic information, will be used to identify the correct age stratum (≤6 or >6 years) for all summaries and analyses that reference age stratum.	Added as a clarification.
6.4.2	Concomitant medications, ASMs, and concomitant rescue medications will be summarized. **The total number of ASMs and concomitant rescue medications will be presented** as well as the number and percentage of patients with at least 1 ASM and rescue medication. ASM listing will also be presented. **A separate summary will be created for the number and percentage of subjects receiving each of the ASMs at baseline.**	Updated content: Concomitant medications, concomitant ASMs, and concomitant rescue medications will be summarized. The number and percentage of patients receiving each ASM concomitantly, and each rescue medication concomitantly will be presented as well as the number and percentage of patients with at least 1 concomitant ASM and concomitant rescue medication. ASM listing will also be presented. Analyses will be based on the data available in electronic data capture (EDC).	Added clarifications. Removed number and percentage of subjects receiving each of the ASMs at baseline as it is deemed unnecessary. ASM at baseline will be continued as concomitant ASM and summary of concomitant ASM will be provided.
6.5.1.3.1	NA	Updated content: A seed value of 14823 will be used for multiple imputation analysis.	Specified seed for reproducibility.

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Table 9.a Summary of changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.5.1.5	NA	New analysis added.	Explore seizure frequency change over time.
6.5.1.3.7	NA	A sensitivity analysis excluding subjects from Ukraine was added.	Explore potential impact of the Russia-Ukraine conflict.
6.5.2.2.2, 6.5.2.5.2, 6.5.4.2, 6.6.3.1	NA	Updated Analysis Windows Table 6.a, Table 6.b, Table 6.c, Table 6.d	Added details to the rules defining analysis windows. In particular, defined an upper bound for analysis V11 window for subjects who rolled over to the OLE study, to ensure data collected after start of OLE is not included in analysis of this study.
6.5.2.2.3 6.5.2.2.3	NA	Added a sensitivity analysis based on multiple imputation under the assumption of MNAR	Provide an alternative to the last-observation-carried-forward (LOCF) method for imputing missing visit V11 scores for Care GI-I and CGI-I scores.
NA	To evaluate the impact of period length in multiple imputations described in Section 6.5.1.3.1, the same approach described in Section 6.5.1.3.1 will be used, with the modification that the full treatment period will be divided into consecutive 7-day periods, except for the last period, which will begin the day after the end of the previous period and end at the day before scheduled V11.	NA (Removed the Section 6.5.1.3.2 in previous version of SAP which contained this sensitivity analysis)	The planned sensitivity analysis described in Section 6.5.1.3.1 is considered adequate to evaluate impact of missingness assumptions on the primary analysis.
6.5.2.2.5	no improvement or worse (scores 4, 5 and 6))	Updated content: no change or worse (scores 4, 5, 6, and 7)	Corrected typographical error and “no improvement” changed to “no change” for better clarity.

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Table 9.a Summary of changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.5.2.3.4, 6.5.2.4.4, 6.5.2.6.4	**no improvement** or worse (scores 4, 5, 6 and 7).	Updated content: no change or worse (scores 4, 5, 6 and 7).	"no improvement" changed to "no change" for better clarity.
6.5.3.4	Heading: Longest **convulsive** Seizure-free Interval Content removed: If a subject has two or more consecutive days of missing seizure diary data, the end of the corresponding MMD seizure-free interval will be the first date of missing seizure diary data, and the next MMD seizure-free interval will begin on the next date that the seizure diary data are available and no MMD seizure occurs.	Updated heading: Longest MMD Seizure-free Interval Updated content: If a subject has one or more consecutive days of missing seizure diary data, the first day of missing seizure diary data will be considered as seizure-free provided it is preceded by a seizure-free day, and all other subsequent days, starting from the second day with missing seizure data, will be assumed to have MMD seizure occurrence, until the next non-missing seizure data are available. Identification of seizure free days will be based on the rules described in Section 9.2.4.	Typographical error corrected. Clarify how a single missing day is handled in the calculation of longest seizure-free interval
6.5.4.1	NA	Added note that seizure types O (Infantile Spasms [Under 3 Years of Age]) and P (Epileptic Spasms [3 Years of Age and Older]) will be grouped into single type in the summary outputs.	Types O and P have similar semiology and therefore are grouped into single item to facilitate clinical interpretation.
6.5.6	NA	Added additional exploratory analyses on subpopulations and seizure types.	These subpopulations and seizure types are clinically relevant to the LGS population and are of scientific interest.
6.6.1	A Treatment-emergent adverse event (TEAE) is defined as any AE	Updated content: A TEAE is defined as	Updated the end date of TEAE collection in relation to the start of the OLE study, to

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Table 9.a Summary of changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
	that starts or increases in severity during or after the first dose of study drug of this study and prior to the first dose of study drug of the OLE for subjects rolling over **immediately** to the OLE **(ie, V11 of the study is combined with V1 of the OLE)**, or through the last study visit for subjects not rolling over **immediately** to the OLE.	any AE that starts or increases in severity during or after the first dose of study drug of this study and prior to the first dose of study drug of the OLE for subjects rolling over to the OLE, or through the last study visit for subjects not rolling over to the OLE.	ensure no duplication in TEAE reporting /collection between this study and the OLE study.
6.6.1	Frequently occurring (≥5% of **all subjects**) TEAEs by PT	Updated content: Frequently occurring (≥5% of **subjects in either one of the treatment groups**) TEAEs by PT	Broadened the definition to allow capturing potentially more TEAEs that may not have been captured under the previous definition of frequently TEAE.
6.6.3.1	**For summary table,** lab results below or equal to lower limit of quantification (LLOQ) will be set to LLOQ/2	Updated content: **Only central lab data will be included in the summary table, and** lab results below or equal to lower limit of quantification (LLOQ) will be set to LLOQ/2	To facilitate interpretation, clarified that numerical summaries only include values from central labs, rather than a mix of central and local labs.
6.6.3.4	Shift table categories and baseline have been redefined	Modify C-SSRS shift table categories and define C-SSRS baseline as the worst of the available measurements prior to initial dose. Refer to Table 6.e. for categories.	Updated categories for shift tables and baseline definition allow more appropriate clinical interpretation

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Table 9.a Summary of changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.6.3.5	NA	Added: "each of ophthalmological evaluations category by left eye, right eye, both eyes and either eye:" V11 window defined with modifications.	Added more details on the analysis. V11 window definition updated based on OLE dates.
6.6.4	Total dose taken, average daily dose, duration of exposure (days), and **total missed doses** will be summarized for all patients by stratum, treatment and overall for the safety analysis set	Updated content: Total dose taken, average daily dose, and duration of exposure (days) will be summarized for all patients by stratum, treatment and overall based on the safety analysis set.	Removed total missed doses removed from summary as it does not provide any interpretable information. Moreover, compliance will be assessed based on dosing diary.
6.6.4	NA	Added content: Summary of maintenance dose categories will be provided.	Added to help assess distribution of maintenance dose.
6.7.2.2	A scatter plot of 24HC percent change from baseline at visit V11/ET vs percent change from baseline in MMD seizure frequency per 28 days will be presented, and **Pearson** correlation will be calculated.	Updated content: A scatter plot of 24HC percent change from baseline at visit V11/ET vs percent change from baseline in MMD seizure frequency per 28 days will be presented, and **Spearman** correlation will be calculated. Exposure-PD analysis will be conducted based on a population PK/PD model and reported separately. The exposure-efficacy analysis will be conducted and reported separately	Spearman correlation is more appropriate. Clarified that Exposure-PD analyses will be reported separately.

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Table 9.a Summary of changes in SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.9	Methodology for the proposed potential blinded interim analysis was removed.	Updated content: The protocol stated that a blinded interim analysis may be performed. However, per sponsor's decision, no interim analysis was or is planned to be conducted.	Per sponsor's decision, no interim analysis was or is planned to be conducted.
9.2.3	NA	Added a section to provide rules to select the right record among multiple records.	Added for clarity and to facilitate programming.
9.2.4	NA	Added a section for seizure diary data handling.	Specify rules for analysis in case of unresolvable seizure diary data conflicts.

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9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate. Minimum and maximum values will be presented to the same number of decimal places as the recorded data. A decimal digit of ≥5 is rounded up away from zero, whereas <5 is rounded down toward zero, to account for rounding of negative numbers. P-values are rounded to 3 decimal places. P-values that would round to 0.000 are presented as <0.001. Seizure frequencies will be rounded to 1 decimal place. BMI will be rounded to 1 decimal place for reporting. Derived questionnaire scores, and other similar efficacy parameters recorded as integers, will be rounded to 1 decimal place for reporting. Averaged lab results (e.g. Diastolic/Systolic Blood Pressure and Pulse [when taken in triplicate]) will be rounded to 1 decimal place for reporting. PK related results will be displayed to the defined level of significant digits.

Percentages will be reported to 1 decimal place, except when the percentage equals exactly 100 where it will be displayed as an integer (100). For zero, only count and no percentage will be displayed.

9.2.2 Definition of Baseline

Unless otherwise stated, baseline values are defined as the last non-missing measurement prior to the first dose of study drug. If multiple measurements are recorded at the same time or time is not available, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered as the baseline value. Both date and time of the measurement and the dosing date and time should be used when determining the baseline if possible. In the case where the last non-missing measurement (except AE and concomitant medications) and the first dose date coincide at the same time, or the same date if time of the measurement is not available, that measurement will be considered as baseline value.

For C-SSRS, the worst value prior to initial dose will be used as the baseline for each question. Life-time values should be included in the baseline derivation. If multiple assessments have the same answer, prioritize "lifetime", and then "12 month", and then "since last visit."

For all efficacy analyses on seizure frequency, baseline refers to the prospective 4- to 6- week baseline period and is defined in Section 6.5.1.1

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9.2.3 Rules to Select a Post-Baseline Record for Summary

Unless otherwise specified, the rules provided below will be followed to select a post-baseline record from an analysis visit window which contains multiple records to report in the summary tables.

Endpoints: Care GI-I, CGI-I, CGI-I Nonseizure Symptoms, CGI-I Seizure Intensity and Duration, QI-Disability, EQ-5D-5L, EQ-VAS

If multiple assessments occur in the same window, the assessment done at the scheduled visit will be mapped to the corresponding analysis visit; ET visits are considered unscheduled visits for this purpose. If only unscheduled visits besides ET are available, the assessment closest to the scheduled visit within the window will be used. An ET visit supersedes other unscheduled visits; i.e., if the corresponding scheduled visit assessment is unavailable but ET visit assessment is available, ET visit assessment will be used for summary regardless of the availability of the other unscheduled visits. If there are two unscheduled assessments within the window and they are equally close to the scheduled visit, the later assessment will be used.

Endpoints: Labs, Vital Signs, ECG

When more than one result for a parameter (e.g. lab test, ECG, etc.) 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 multiple measurements are recorded on the same day, and the collection time of at least one assessment is missing, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be used.

For shift summary, both central and local lab 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.

For shift tables of ECG, if multiple interpretations are available within the same window, the worst (most severe) interpretation will be used for cross-tabulation of shift. The order for ECG interpretation in decreasing order of severity is: abnormal clinically significant, abnormal not clinically significant, within normal limit, not evaluable

Endpoint: C-SSRS

If there are multiple records in an analysis window, the latest value within the window will be selected for summary; if multiple assessments are available at the same time, the worst value (for each question) will be used for summary.

9.2.4 Handling of Seizure Diary Data

Seizure data are collected via the seizure diary, including the date of seizure, and the Yes/No/Unknown response on whether a day was seizure free.

- If no seizures are entered for a day and a "Yes" response is given on whether that same day was seizure free, the number of seizures for that day is 0. That day will be counted as seizure free day.
- If no seizures are entered for a day and a "Yes" response is not given on whether that same day was seizure free, seizure data for that day will be considered missing. For example, if only a response of "Unknown" or "No" is given on whether a day was seizure free, but no seizures are entered for that day, seizure data for that day will be considered missing. That day will not be counted as seizure free day.
- If no seizures are entered for a day and seizure diary has "Yes" or "No" (or "Unknown") as response given on whether that day was seizure free, then the "Yes" response for that day supersedes any other responses on the same day, i.e., the number of seizures for that day is considered 0. That day will be counted as seizure free day.
- If seizures are entered for a day, the seizures recorded for that day supersede any "Yes" or "Unknown" responses given on whether that same day was seizure free. That day will not be counted as seizure free day.
- 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.

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9.3 Analysis Software

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

9.4 Seizure Classifications Collected in Daily Seizure Diary

Primary Outcome Seizure Types: Major Motor Drop (MMD)	
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., Hypermotor 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

Non-Primary Outcome Seizure Types	
I - Focal Without Motor Signs J - Focal with Minor Motor Signs (e.g., Lip Smacking, Eyelid Fluttering, Automatisms Only) K - Absence L - Tonic Seizures Without Fall or Without Likely Fall (e.g., Head Drop or Upper Extremities Only)	M - Atonic Seizures Without Fall or Without Likely Fall (e.g., Head Drop or Upper Extremities Only) N - Myoclonic O- Infantile Spasms (Under 3 Years of Age) P - Epileptic Spasms (3 Years of Age and Older) Q - Non-Convulsive Status Epilepticus R – Other

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9.5 Health Outcome Scales

9.5.1 QI-Disability Domains

Domain	**Item**
Social interaction	Expressed happiness when they were understood
	Appeared relaxed when making eye contact
	Initiated greetings with people verbally or nonverbally (e.g. eye contact)
	Enjoyed being included
	Enjoyed the social experiences of meal times
	Responded positively when others paid attention to them (e.g. your child smiled, showed interest)

Domain	Item
	Showed pleasure or excitement when looking forward to activities (e.g. going to school, outings, events)
Positive emotions	Been in a good mood
	Smiled or brightened their facial expression
	Showed happiness through body language (e.g. making eye contact, body facing others)
	Showed cheeky or comical mannerisms (e.g. laughed, giggled)
Physical health	Had enough energy to participate in daily routines and activities
	Kept in good general health (e.g. avoided coughs, colds, fever)
	Slept well during the night
	Been alert and aware during the day
Negative emotions	Been unsettled without an apparent reason
	Showed aggression (e.g. hitting, kicking, using offensive language, being destructive)
	Appeared upset or angry (e.g. crying, screaming, moving or stiffening the body)
	Become withdrawn with a low mood
	Deliberately hurt themselves
	Expressed discomfort with changes in routine (e.g. carers, school, respite, out-of-home care)
	Showed signs of being anxious or agitated (e.g. teeth grinding, fast breathing, avoidance)
Leisure and the outdoors	Enjoyed moving their body (e.g. crawling, walking, swinging, swimming)
	Enjoyed feeling steady or stable during physical activities (e.g. sitting, standing, bike riding)
	Enjoyed physical activities (e.g. going out for a walk, swimming, swinging, dancing)
	Enjoyed going on outings in the community (e.g. shopping, party, sports, theatre)

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Domain	Item
	Enjoyed spending time outdoors (e.g. contact with water, grass, wind, sunshine)
Independence	Expressed their needs (e.g. hunger, thirst, toileting)
	Made their own choices for activities or things they enjoy (e.g. DVDs, toys)
	Helped to complete routine activities (e.g. dressing, feeding)
	Enjoyed making things with their hands – can be with help (e.g. building blocks, painting, cooking)
	Enjoyed using technology (e.g. computer, tablet, applications on phones)

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