# Statistical Analysis Plan

NCT Number: NCT04940624

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 Dravet Syndrome (DS)

Study Number: TAK-935-3001

Document Version and Date: Original, 29 March 2022

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# STATISTICAL ANALYSIS PLAN

Study Number: TAK-935-3001 (SKYLINE)

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 Dravet Syndrome (DS)

Phase 3

Version: Original

Date: 29 March 2022



Prepared by:

[redacted] PhD

[redacted], Neuroscience Statistics

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|---|---|---|
| Original | 29 Mar 2022 | Not applicable |

**TABLE OF CONTENTS**

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES

## ABBREVIATIONS

| | |
|---|---|
| [redacted] | [redacted] |
| 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 |
| DS | Dravet syndrome |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EMA | European Medicines Agency |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| GCP | good clinical practice |
| IEC | institutional review board |
| IRB | independent ethics committee |
| ITT | intent-to-treat |
| LLOQ | lower limit of quantification |
| LOCF | last-observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent-to-treat |
| OLE | open-label extension |
| QI-Disability | Quality of Life Inventory-Disability |
| PBO | placebo |
| PEG | percutaneous endoscopic gastrostomy |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| PT | Preferred Term |
| PTE | pretreatment event |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| [redacted] | [redacted] |

| | |
|---|---|
| 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 convulsive 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 convulsive seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.*

### 1.1.2 Secondary Objective(s)

*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 convulsive 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 convulsive seizure-free days.*
- *Longest convulsive seizure-free interval.*
- *Number of days when rescue 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 Non-seizure Symptoms completed by clinician with input from the caregiver.*
- *Effect on Quality of Life Inventory-Disability (QI-Disability).*

### 1.1.3 Additional Objective(s)

#### *1.1.3.1 Exploratory Objectives*

[redacted]

*1.1.3.2 Safety Objectives*

- *To assess the incidence of TEAEs.*
- *To assess the incidence of abnormal values and change for clinical laboratory evaluations, vital signs, electrocardiogram (ECG) parameters, and Columbia-Suicide Severity Rating Scale (C-SSRS) parameters.*
- *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 Endpoint(s)

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

### 1.2.2 Secondary Endpoint(s)

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

### 1.2.3 Exploratory Endpoints

[redacted]

### 1.2.4 Safety Endpoints

- *Incidence of TEAEs.*

- *Incidence of abnormal values for clinical laboratory evaluations, vital signs, C-SSRS, and ECG parameters.*
- *Change from baseline in clinical laboratory evaluations, vital signs, C-SSRS, ECG, and ophthalmological evaluations.*
- *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.



**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 convulsive seizure frequency per 28 days during the Full Treatment Period.<br><br>For EMA registration:<br>Percent change from baseline in convulsive 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.<br><br>For EMA registration:<br>The principal stratum strategy will be used to 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. | 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. |

### 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.

**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:**<br>*The proportion of treatment responders defined as those with ≥50% reduction in convulsive seizures from baseline during* the Full Treatment Period.<br>For EMA registration:<br>*Proportion of treatment responders defined as those with ≥50% reduction in convulsive seizures from baseline during* the Maintenance Period. | **Variable:**<br>Binary variable indicating whether the subject is a treatment responder during the Full Treatment Period (or Maintenance Period for EMA registration).<br>**Strategy for Addressing Intercurrent Events:**<br>All anticipated intercurrent events will be addressed using the treatment policy strategy.<br>For EMA registration:<br>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<br>**Population-Level Summary:**<br>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**<br>*Effect on the Caregiver Global Impression of Improvement (Care GI-I).* | **Variable:**<br>Response on the 7-point Care GI-I scale at the end of the Full Treatment Period.<br>**Strategy for Addressing Intercurrent Events:**<br>All anticipated intercurrent events will be addressed using the treatment policy strategy.<br>**Population-Level Summary:**<br>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. |

## Table 1.b Attributes of Secondary Estimands

| | |
|---|---|
| **Secondary #3**<br>*Effect on the Clinical Global Impression of Improvement* (CGI-I) (clinician). | **Variable:**<br>Response on the 7-point CGI-I scale at the end of the Full Treatment Period.<br>**Strategy for Addressing Intercurrent Events:**<br>All anticipated intercurrent events will be addressed using the treatment policy strategy.<br>**Population-Level Summary:**<br>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**<br>*Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregiver.* | **Variable:**<br>Responses on the three domains (the testing order will be: alertness, communication, and disruptive behaviors) of the CGI-I Nonseizure Symptoms scale at the end of the Full Treatment Period.<br>**Strategy for Addressing Intercurrent Events:**<br>All anticipated intercurrent events will be addressed using the treatment policy strategy.<br>**Population-Level Summary:**<br>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**<br>*Effect on Quality of Life Inventory-Disability (QI-Disability).* | **Variable:**<br>Change from baseline in QI-Disability total score at the end of the Full Treatment Period.<br>**Strategy for Addressing Intercurrent Events:**<br>All anticipated intercurrent events will be addressed using the treatment policy strategy.<br>**Population-Level Summary:**<br>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. |

**Table 1.b Attributes of Secondary Estimands**

| **Secondary #6** | **Variable:** |
|---|---|
| *Effect on CGI-I Seizure Intensity and Duration.* | 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. |

# 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 young adult subjects with DS. 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 142 male and female pediatric and young 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:*

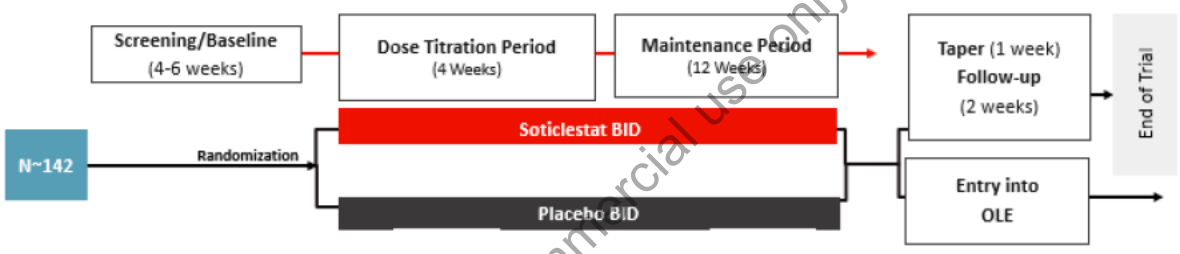
- *4- to 6-week screening/baseline period.*
- *16-week treatment period.*
  - *4-week titration period.*
  - *12-week maintenance period.*
- *1-week taper period for those discontinuing study drug, followed by a 2-week safety follow-up visit or phone call.*

*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 percutaneous endoscopic gastrostomy (PEG) tube. A jejunostomy tube (J-tube) may be considered following approval by the medical monitor or sponsor. Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.*

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

**Figure 2.a Schematic of Study Design**






*All doses will be blinded; subjects on soticlestat or placebo 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 Table 2.a through Table 2.d).*

*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 (ie, on study Day 2). The dosing schedules by weight are shown in Table 2.a through Table 2.d. The minimum dose allowed during the study is 100 mg BID (weight-based dosing <45 kg). Subjects who cannot tolerate the minimum dose will be discontinued from the study. Subjects weighing <45 kg will be dispensed 20 mg mini-tablets 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.*



### *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.*



## 2.2 Dose Titration Period (4 Weeks)

*Subjects will receive the initial dose of study drug (Dose 1) for the first 7 days after randomization at Visit 2. Study drug dose will be increased to Dose 2 and Dose 3 every 7 days. If the subjects do not experience any tolerability issues, they will remain on Dose 3 for the remaining 7 days 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; 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

*Dose taper for early discontinuation or completion of the double-blind study will occur for subjects not rolling over to OLE study, followed by a 2-week safety follow-up. During the taper period, the study drug dose will be tapered down to a lower dose (taper Dose 3 to Dose 2, taper Dose 2 to Dose 1) every 3 days until the study drug dose is discontinued. After tapering, the subject/caregiver will complete a safety follow-up phone call (or visit) approximately 14 days after the last dose of study drug and exit the study.*

*Subjects who discontinue study drug treatment before the completion of the study will continue to be followed per protocol and at minimum maintain daily seizure diary until completion of the study related procedures.*

*Following completion of the study, subjects will have the option to enroll in the OLE study as per the study's inclusion/exclusion criteria.*

# 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:**<br>*To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to standard of care (SOC) as compared with placebo during the full treatment period (titration + maintenance).*<br>*For EMA registration:*<br>*To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.* | The distribution of percent change from baseline in convulsive 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 |
|---|---|---|
| **Secondary #1:**<br>*Proportion of treatment responders defined as those with ≥50% reduction in convulsive seizures from baseline during* the full treatment period.<br>For EMA registration:<br>*Proportion of treatment responders defined as those with ≥50% reduction in convulsive 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**<br>*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**<br>*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**<br>*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. |
| **Secondary #5**<br>*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. |

**Table 3.a Statistical Hypotheses**

| Study objective | Statistical null hypothesis | Criteria for positive outcome |
|---|---|---|
| **Secondary #6**<br>*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. |

## 3.2 Multiplicity Adjustment

The global type 1 error will be controlled 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 142 subjects at a 1:1 ratio to receive soticlestat or placebo, resulting in approximately 71 subjects per arm. A minimum of 20 pediatric subjects aged 2 through 6 years will be enrolled. The sample size calculation is based on the results from the ELEKTRA study and other studies on seizure frequency reduction in subjects with DS and under the assumption of using the Wilcoxon rank-sum test. The pooled SD of the percent change from baseline in convulsive seizure frequency is 55%. It is assumed that subjects in the placebo group will experience a mean reduction from baseline in convulsive seizure frequency of 5%. A sample size of 71 subjects per treatment arm will provide at least 80% power at a 2-tailed significance level of 5% to detect a 27% difference in mean percent reduction in convulsive seizure frequency per 28 days during the 16-week treatment period between treatments (assuming subjects receiving soticlestat will experience at least a 32% mean reduction in convulsive seizure frequency).*

# 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 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 [redacted]

[redacted]

### 5.5 [redacted]

[redacted]

## 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, [redacted] 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.

#### 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, [redacted] analysis sets.

## 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 Demographic Characteristics

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

### 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, 4 etc.
- Convulsive seizure frequency during Baseline Period
- All seizure frequency during Baseline Period
- Ketogenic/ modified Atkins Diet
- Vagus nerve stimulation
- [redacted]

### 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.*

*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

*Prior medications include all treatment including but not limited to herbal treatments, vitamins, surgical implants and prescribed medications received within 6 months prior to signing of informed (e)consent and must be recorded in the eCRF.*

*All prior ASMs previously taken and discontinued prior to signing of informed consent must be recorded in the eCRF.*

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.*

*Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version* Global B3 2021.03*). A by-subject listing of concomitant medications will include all medications (including vaccinations) taking 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.*

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 number and percentage of subjects receiving each of the ASMs at baseline.

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 convulsive 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 convulsive seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the maintenance period*

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.*

Convulsive seizures consist of the following 5 seizure types, which are among the seizure classifications approved for this study by TESC. For the efficacy analyses by seizure type, any convulsive 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) rather than under the category of Status Epilepticus. Any convulsive seizure type lasting 30 minutes or longer will be captured under the category of Status Epilepticus.

| **Primary Outcome Seizure Types: Convulsive Seizures** | |
|---|---|
| A - Hemiclonic or Focal Clonic | D - Bilateral Clonic |
| B - Focal to Bilateral Tonic-Clonic | E - Convulsive Status Epilepticus |
| C - Generalized Tonic-Clonic | |



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 convulsive seizures.

### *6.5.1.2 Main Analytical Approach*

The primary efficacy analysis will compare percent change from baseline in frequency of convulsive seizures 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 convulsive seizures per 28 days during the Full Treatment Period (Maintenance Period for EMA registration) as the outcome variable and treatment group, age stratum (≤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 convulsive seizure frequency per 28 days during the Full Treatment Period (Maintenance Period for EMA registration) between the soticlestat and placebo treatment groups. The asymptotic 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 6.5.1.3.6. [redacted].

Descriptive summaries of convulsive 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 convulsive seizure frequency per 28 days during the Full Treatment Period and the Maintenance Period.

*6.5.1.3* [redacted]

[redacted]

*6.5.1.3.1* [redacted]

[redacted]

6.5.1.3.2 [redacted]

*6.5.1.3.3* [redacted]

*6.5.1.3.4* [redacted]

*6.5.1.3.5* [redacted]

*6.5.1.3.6* [redacted]

[redacted]

[redacted]

*6.5.1.3.7* [redacted]

[redacted]

*6.5.1.4* [redacted]

[redacted]

### 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 convulsive seizure frequency per 28 days during the Full Treatment Period are considered responders.

For EMA registration:

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

The method of calculating percent change from baseline in convulsive 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 procedure FREQ.

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

*6.5.2.1.3* [redacted]

[redacted]

[redacted]

*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 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. 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 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. If multiple assessments occur in the same window, the assessment done at the scheduled visit will be mapped to the corresponding visit; if only unscheduled visits are available, the last assessment within the window will be used.

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

| Analysis Visit | Analysis Visit Window |
|---|---|
| V8 | The next day of the initial dose – the midpoint between the scheduled V8 and V11 |
| V11 | > the midpoint between the scheduled V8 and V11 |

*6.5.2.2.3* [redacted]

[redacted]

*6.5.2.2.4* [redacted]

[redacted]

*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. 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.

#### *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* [redacted]

[redacted]

#### *6.5.2.3.4* [redacted]

[redacted]

### *6.5.2.4 Secondary Endpoint Analysis: CGI-I Non-Seizure 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.

#### *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* [redacted]

[redacted]

*6.5.2.4.4* [redacted]

[redacted]

### *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.

#### *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. Each assessment will be mapped to either Analysis Visit Number 1 or 2 according to Table 6.b. If multiple assessments occur in the same window, the assessment done at the scheduled visit will be mapped to the corresponding visit; if only unscheduled visits are available, the last assessment within the window will be used. Analysis Visit 2 will be considered the End of Treatment Visit. 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 Visit 2 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 Baseline, Analysis Visit 1, and Analysis Visit 2 will be provided.

**Table 6.b Analysis Windows for QI-Disability**

| Analysis Visit Number | Analysis Visit Window |
|---|---|
| 1 | < Analysis Day 57 |
| 2 | ≥ 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 convulsive 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. 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.

##### *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* [redacted]

[redacted]

*6.5.2.6.4* [redacted]

[redacted]

### 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 convulsive 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 convulsive 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.



#### *6.5.3.3 Change from Baseline in Proportion of Convulsive Seizure-free Days*

The proportion of convulsive seizure-free days during a period is define as the number of non-missing seizure diary days when no convulsive seizures occurred during the period divided by the number of non-missing seizure diary days during the period. The proportion of convulsive 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 convulsive 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 convulsive seizure-free days will 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 Convulsive Seizure-free Interval*

The longest convulsive seizure-free interval is defined as the longest consecutive number of days during the Full Treatment Period on there were no convulsive seizures. If a subject has two or

more consecutive days of missing seizure diary data, the end of the corresponding convulsive seizure-free interval will be the first date of missing seizure diary data, and the next convulsive seizure-free interval will begin on the next date that the seizure diary data are available and no convulsive seizure occurs. The longest convulsive seizure-free interval will be summarized descriptively by treatment group. The treatment effect on the longest convulsive 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.

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.



### 6.5.4 Exploratory Endpoints Analysis

*6.5.4.1* [redacted]

*6.5.4.2* [redacted]

*6.5.4.3* [redacted]

### 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 that not including age stratum as a predictor in the rank ANCOVA model.

## 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.

### 6.6.1 Adverse Events

*A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.*

*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.*

*PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.*

*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 Treatment-emergent adverse event (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 immediately to the OLE (i.e., V11 of this study is combined with V1 of the OLE), or through the last study visit for subjects not rolling over immediately 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).

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. 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. The tables will include number of events, as appropriate. Summary tables that will be generated will include, but may not be limited to:

- Overall TEAEs
- TEAEs by SOC and PT

- Frequently occurring (≥5% of all subjects) TEAEs by PT: the 5% cut-off value will be applied to total before rounding
- TEAEs by Maximum Severity, SOC and PT
- Drug-Related TEAEs by SOC and PT
- TEAEs leading to 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.



### 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 events 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 both SI units and conventional (CV) units, if available. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets. All summaries and analyses will be based on the values using these preferred SI units.

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. Study baseline will be used for change from baseline. Measurements will be summarized by nominal timepoints. For summary table, 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. A window approach (see Table 6.c) will be used to define the timepoints included in the summary. When more than one result for a parameter is obtained in a visit window, the latest one will be used. If multiple measurements are recorded at the same time, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be used.

Shift tables for Hematology and Chemistry qualitative parameters will be created.

**Table 6.c Analysis Windows for Laboratory Evaluations Summary**

| Analysis Visit | Analysis Visit Window |
|---|---|
| Baseline | Predose – Day of the initial dose |
| V9 | The next day of the initial dose – the midpoint between the scheduled V9 and V11 |
| V11 | > the midpoint between the scheduled V9 and V11 |



For Urinalysis, the parameters to be analyzed includes pH, protein, glucose, ketones, bilirubin, erythrocytes and leukocyte esterase. These parameters will be summarized by treatment group, and overall in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit. The aforementioned window approach specified in Table 6.c will be used.

Listings of all clinical safety laboratory data will be provided in both SI and CV units (if available). Laboratory data outside of the normal reference range will be indicated in the listings. 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.

#### *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. The same window approach as described in Section 6.6.3.1 will be used.

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. The same window approach as described in Section 6.6.3.1 will be used. 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.

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.

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 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.

Suicidal ideation is defined as a "Yes" answer to any one of the five suicidal ideation questions (categories 1-5) on the C-SSRS. Suicidal behavior is defined as a "Yes" answer to any one of the five suicidal behavior questions (categories 6-10) on the C-SSRS. Suicidal ideation or behavior is defined as a "Yes" answer to any one of the ten suicidal ideation and behavior questions (categories 1-10). The baseline of C-SSRS will be the last measurement prior to initial dose of study drug. If the screening measurement is the only measurement prior to initial dosing, then the worst value will be used as the baseline.

For each visit, number and percentage of subjects with suicidal ideation, suicidal behavior, and the number and percentage of subjects who have "Yes" answers of the ten suicidal ideation and behavior questions will be summarized by treatment group. For post-dose visits, the same window as described in Table 6.c will be used. If multiple assessments occur after the initial

dosing, the assessment done at the scheduled visit will be mapped to the corresponding visit; if only unscheduled visits are available, the last post-dose assessment within the window will be used.

Shifts in C-SSRS will be presented as cross-tabulation (baseline versus maximum post-baseline category) of numbers and percentages of subjects of no suicidal ideation or behavior, suicidal ideation without suicidal behavior, suicidal behavior and missing by treatment group. Each subject is counted once, subjects with both suicidal ideation and suicidal behavior will be included in the suicidal behavior category.

C-SSRS data will also be listed.

#### *6.6.3.5 Ophthalmological Evaluations*

Ophthalmological evaluations will be done at V1 and V11, 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 contacted within a 14-day window before V11.

For each eye, the data of the following items will be summarized in terms of number and percentage of subjects in each category:

- 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

For the above summaries, if multiple post-baseline measurements are available, the last post-baseline measurement will be mapped to V11. If multiple measurements are recorded on 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.*

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 dose (all non-missed doses are considered full dose).

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. Also, number and percentage of subjects in each final maintenance dose categories (dose 1, dose 2 and dose 3 in *Table 2.a* - *Table 2.d*) will be summarized.

Study medication data will be collected by the case report form and also by the number of tablets returned. The primary method of assessing compliance will be based on the number of returned tablets.

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

1. Using the 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 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% unless there is a valid reason for interruption) or not will be summarized.

All study drug administration and compliance data will also be listed.

**6.7** [redacted]

**6.7.1** [redacted]

[redacted]

*6.7.1.1* [redacted]

[redacted]

*6.7.1.2* [redacted]

[redacted]

**6.7.2** [redacted]

[redacted]

*6.7.2.1* [redacted]

[redacted]

*6.7.2.2* [redacted]

[redacted]

**6.8** [redacted]

**6.8.1** [redacted]

[redacted]

## 6.9 Interim Analyses

No interim analyses are planned for this study.

## 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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2. Frangakis CE, Rubin DB. Principal Stratification in Causal Inference. Biometrics. 2002 Mar;58(1):21–9.
3. Lou Y, Jones MP, Sun W. Estimation of causal effects in clinical endpoint bioequivalence studies in the presence of intercurrent events: noncompliance and missing data. Journal of Biopharmaceutical Statistics. 2019 Jan 2;29(1):151–73.
4. Chiba Y, VanderWeele TJ. A Simple Method for Principal Strata Effects When the Outcome Has Been Truncated Due to Death. American Journal of Epidemiology. 2011 Apr 1;173(7):745–51.

## 8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

| Change from planned analysis specified in the protocol | Rationale |
|---|---|
| [redacted] | [redacted] |
| The main analytic approach for QI-Disability was changed from ordinal logistic regression to MMRM. | • QI-Disability is a continuous endpoint and MMRM analysis was considered more appropriate. |
| The order of gatekeeping procedure on the secondary endpoints was changed to: responder rate, Care GI-I, CGI-I (clinician), CGI-I Nonseizure Symptoms, QI-Disability, and CGI-I Seizure Intensity. | • Alignment with sponsor goals |
| [redacted] | |
| [redacted] | |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

# 9.0 APPENDIX

## 9.1 Changes From the Previous Version of the SAP

Not applicable.

## 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. BMI should 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. [redacted]

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 before the first dose of study drug. If multiple measurements are recorded on 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 the 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 coincide at the same time, or the same date if time of the measurement is not collected, that measurement will be considered as baseline value. For 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.

## 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** | |
|---|---|
| A - Hemiclonic or Focal Clonic | D - Bilateral Clonic |
| B - Focal to Bilateral Tonic-Clonic | E - Convulsive Status Epilepticus |
| C - Generalized Tonic-Clonic | |
| **Non-Primary Outcome Seizure Types** | |
| 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 | K - Absence |
| G - Tonic Seizures Involving Major Body Areas such as Lower Extremities or Trunk Leading to Fall or Likely Fall | L - Tonic Seizures Without Fall or Without Likely Fall (e.g., Head Drop or Upper Extremities Only) |
| H - Atonic Seizures Involving Major Body Areas such as Lower Extremities or Trunk Leading to Fall or Likely Fall | M - Atonic Seizures Without Fall or Without Likely Fall (e.g., Head Drop or Upper Extremities Only) |
| I - Focal Without Motor Signs | N - Myoclonic |
| J - Focal with Minor Motor Signs (e.g., Lip Smacking, Eyelid Fluttering, Automatisms Only) | O - Infantile Spasms (Under 3 Years of Age) |
| | P - Epileptic Spasms (3 Years of Age and Older) |
| | Q - Non-Convulsive Status Epilepticus |
| | R - Other |



## 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) |
| | Showed pleasure or excitement when looking forward to activities (e.g. going to school, outings, events) |

| Domain | Item |
|---|---|
| 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) |
| | 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) |

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| [redacted] | Biostatistics Approval | 30-Mar-2022 19:40 UTC |