Clinical Study Protocol

NCT Number: NCT03635073

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

Study Number: TAK-935-18-001

Document Version and Date: Amendment 4, 24 Aug 2021

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

TAKEDA PHARMACEUTICALS

PROTOCOL

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

Open-Label Extension Study of Soticlestat in Developmental Epileptic Encephalopathies

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	TAK-935-18-001		
IND Number:	133627	**EudraCT Number:**	2018-002485-39
Compound:	Soticlestat (TAK-935)		
Date:	24 August 2021	**Version/Amendment Number:**	Amendment 4

Amendment History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
24 August 2021	Amendment 4	Substantial	Global
14 August 2020	Amendment 3	Substantial	Global
13 February 2020	Amendment 2	Substantial	Global
28 May 2019	Amendment 1 ES v1	Substantial	Spain
11 February 2019	Amendment 1	Substantial	Global
16 April 2018	Initial version	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

TDC-sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines are provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study contact list.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

[redacted] MD Soticlestat Program Neuroscience Therapeutic Area Unit Takeda	Date
[redacted] PhD Statistical and Quantitative Sciences Takeda	Date

INVESTIGATOR AGREEMENT.

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, life, dignity, integrity, confidentiality of personal information, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.2 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the Investigator. (Appendix D).

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 4 Summary of Changes

Rationale for Amendment 4

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reasons for this amendment are to reflect change of sponsor, correct errors, and simplify the protocol to maximize subject retention.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only, and are not captured in the following table. The following table summarizes the changes.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Cover page. Throughout text.	Change name of sponsor from Ovid Therapeutics Inc. to Takeda Development Center Americas, Inc.	Ovid is no longer involved in development of soticlestat.
2.	Cover page, page headers, Section 2.0, Study Summary	Remove (OV935) from study title and number.	Ovid is no longer involved in development of soticlestat.
3.	Cover page Section 2.0, Study Summary Section 9.1.2 Informed Consent Procedures	Rename ENDYMION to ENDYMION 1.	Change in recognition of the ENDYMION 2 study (TAK-935-3003) planned for phase 3 subjects.
4.	Title and page headers. Change throughout, except for study numbers.	Change TAK-935 to Soticlestat (TAK-935). Replace TAK-935 with soticlestat in text.	Soticlestat has been approved as the International Nonproprietary Name for TAK-935.
5.	Section 1.2, Approval	Change signatories to Takeda.	Identify current sponsor.
6.	Section 2.0, Study Summary	Remove description of exploratory objectives and endpoints from synopsis.	To comply with the Takeda template.
7.	Section 2.0, Study Summary	Clarify that screening/baseline period of 4 weeks is the maximum.	Clarify maximum allowed gap between antecedent study and this study.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
8.	Section 3.0, Study Reference Information Section 3.2, Coordinating Investigator Section 6.0, Study Design and Description Section 7.3, Concomitant Medications Section 7.4.1, Criteria for Discontinuation or Withdrawal of a Subject Section 8.0, Clinical Study Material Management Section 9.0, Study Plan Section 9.4, Laboratory Sample Collection Section 11.0, Study-Specific Committees Appendix A, Schedule of Study Procedures Appendix D, Responsibilities of the Investigator	Add sections used in the Takeda protocol template that were not covered in the original protocol developed by Ovid Therapeutics Inc; change headings to Takeda terminology.	To comply with the Takeda template.
9.	Section 4.1, Background Section 4.2, Study Rationale	Update with information on recently completed studies.	Bring context up-to-date.
10.	Section 2.0, Study Summary Section 5.1.2, Secondary Objectives Section 5.1.3, Exploratory Objective	[redacted]	[redacted]
11.	Section 5.1.3, Exploratory Objective Section 5.2.3, Exploratory Endpoints	[redacted]	[redacted]
12.	Section 2.0, Study Summary Section 5.2.2, Secondary Endpoints Section 5.2.3, Exploratory Endpoints	[redacted]	[redacted]

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	Section 2.0, Study Summary	Remove reference to coronavirus disease 2019 (COVID-19) procedures in synopsis.	This detail unnecessary for protocol synopsis.
14.	Section 2.0, Study Summary Section 13.2, Determination of Sample Size	Reduce enrollment expectation.	Previously included rollover phase 3 subjects in the estimate. Now phase 3 subjects who consent will be rolled over to planned ENDYMION 2 open-label extension study.
15.	Section 7.4.1, Criteria for Discontinuation or Withdrawal of a Subject	Expand criteria for discontinuation of subjects.	To comply with the Takeda template.
16.	Section 7.4.1, Criteria for Discontinuation or Withdrawal of a Subject	For subjects who do not undergo the Baseline Period in this study, only the seizure frequency from the Baseline Period of the antecedent study will be used as the baseline for determining increase in 28-day seizure frequency, not the historical baseline seizure frequency from the last 3 months before entering the study.	Clarify the baseline for determining increase in 28-day seizure frequency.
17.	Section 8.1, Materials and Supplies Section 8.1.1, Storage	Remove country-specific material.	Country-specific information will be included in site materials.
18.	Section 8.2.1, Subjects Who Complete Antecedent Studies >15 Days Before Screening in This Study	Remove seizure diary data collected during the antecedent study as baseline.	Clarify that the seizure diary data collected during the 4-week Baseline Period will be used as the baseline for endpoint analysis in this study.
19.	Section 9.1.1, COVID-19 Pandemic Study Procedures Appendix C, Study Management During COVID-19 Pandemic	Replace text of Appendix C, Study Management During COVID-19 Pandemic, with equivalent Takeda language	To comply with the Takeda template.
20.	Throughout Section 9.1, Study Procedures	Where remote assessments are permitted, clarify that these can be by video, phone, or telehealth/telemedicine.	Clarify allowable means of performing remote assessments.

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Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
21.	Section 9.1.11, Procedures for Clinical Laboratory Samples	Move table of laboratory tests here (previously in appendix). Remove references to maximum blood volumes and literature reference. Remove prior Appendix B, with blood sample volumes.	This will be described in the laboratory manual.
22.	Section 9.5, [redacted]	[redacted]	Consistency with other protocols.
23.	Section 13.3, Definition of Baseline	Baseline is defined as the baseline of the antecedent study.	Clarify the definition of baseline for statistical analyses.
24.	Section 13.4.2, Intent-to-Treat Analysis Set Section 13.4.3, Modified Intent-to-Treat Analysis Set	Define intent-to-treat and modified intent-to-treat analysis sets.	Make analysis sets consistent with other studies.
25.	Section 15.0, List of References	Remove *Howie S. Blood sample volumes in child health research: review of safe limits. Bulletin of the World Health Organization, 2011;89:46-53* from references list.	Removed by edits to Section 9.1.11, Procedures for Clinical Laboratory Samples via Local Laboratory.
26.	Appendix B, Strong CYP3A Inducers and Inhibitors	Update the list of strong cytochrome P450 (CYP)3A inducers and inhibitors.	Prior list was incomplete.
27.	Appendix D, Responsibilities of the Investigator	Add Takeda appendices for this topic.	To comply with the Takeda template.
28.	Appendix E, Protocol History	Add appendix of protocol amendment history.	To comply with the Takeda template.

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LIST OF IN-TEXT TABLES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Soticlestat (TAK-935)	
Title of Protocol: A Phase 2, Prospective, Interventional, Open-Label, Multi-Site, Extension Study to Assess the Long-Term Safety and Tolerability of Soticlestat (TAK-935) as Adjunctive Therapy in Patients with Developmental Epileptic Encephalopathies Including Dravet Syndrome, Lennox Gastaut Syndrome, CDKL5 Deficiency Disorder, and Chromosome 15 Duplication Syndrome (ENDYMION 1)	**IND No.:** 133627	**EudraCT No.**: 2018-002485-39
Study Number: TAK-935-18-001	**Phase:** 2	

Study Design:

This is a multisite, open-label extension (OLE) study designed to obtain additional safety and tolerability data related to soticlestat (also known as TAK-935) administered long-term in subjects with developmental and epileptic encephalopathies who participated in a previous soticlestat clinical study. Additional aims are to explore the long-term effects of soticlestat on seizure frequency and to assess the effects of soticlestat on quality-of-life measures.

All subjects will receive soticlestat twice a day (BID), with or without food, orally 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 and sponsor. Subjects enrolled in clinical sites in China are not to receive study drug via G-tube, PEG tube, or J-tube. No subject will receive placebo treatment in this OLE study. The planned doses of soticlestat represent the intended therapeutic doses of soticlestat and include the full range of doses available for soticlestat. The maximum dose available for this study will be 600 mg/day (300 mg BID).

Subjects from 3 antecedent studies (TAK-935-2001, TAK-935-2002, and TAK-935-18-002) will be rolled over into this study. Subjects will be eligible for screening within 15 days of completing the last visit of the antecedent soticlestat study (except for adult subjects enrolled in the TAK-935-2001 study, who will be eligible for screening in this OLE study up to 15 months after completion of the antecedent study). A subject who completes the antecedent study between approximately 15 and 30 days before the Screening Visit of this OLE study can be entered in this study with the approval of the sponsor after considering the subject's overall compliance in the antecedent study and after the subject meets all inclusion and no exclusion criteria for this study.

Study design, including timing of enrollment and dosing and titration schedule, is based upon the age of the subject (pediatric or adult), the type of antecedent study completed (blinded or unblinded), and how many days elapsed between completing the antecedent study and the Screening Visit in this study (≤15 days or >15 days). The last visit in the antecedent study can be combined with the first visit in this OLE.

Study procedures for subjects who complete antecedent studies >15 days before screening are as follows:

- 4-week Screening/Baseline Period.
- 2-week Dose Optimization Period (see Dosing and Titration Schedule, below).
- Maintenance Period that continues until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor.
- 4-week Safety Follow-up Period of soticlestat dose tapering (up to 2 weeks) and safety follow up.

At the Screening Visit (Visit 1), informed consent and/or assent (if applicable) is obtained from the subjects and/or subjects' legally acceptable representative. Subjects will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria. Identical assessments for subjects who complete the last visit of their antecedent protocol ≤30 days before the Screening Visit in this study do not need to be repeated. At this Screening Visit and at subsequent visits, subjects and/or subjects' caregivers will be provided with a seizure diary and will be instructed to record seizure data on a daily basis. The 4-week Baseline Period seizure diary recording can begin the day after informed consent has been signed. At the end of the 4 week Baseline Period, subjects will return to the clinic on Visit 2 (Day 1).

Dosing and Titration Schedule

Subjects will initiate soticlestat at Dose 1, and the dose will be titrated up every 7 days (Day 8 and Day 15) as shown in the table below. Two days after each change in dose, subjects will be contacted by phone to monitor study drug compliance, concomitant medication use, and AEs. Subjects who cannot tolerate Dose 1 will be withdrawn from the study. After up-titration, subjects who cannot tolerate the new dose may have their dose reduced, based on the investigator's judgment and in consultation with the subject's caregiver, when applicable. Subjects will be contacted by phone 2 days following escalation to the maximum dose to assess safety and tolerability of the study drug. Dosing may be adjusted at the investigator's discretion throughout the study; however, frequent adjustments are discouraged.

Adult subjects who cannot tolerate at least 100 mg BID dosing will be withdrawn from the study. Pediatric subjects who cannot tolerate Dose 1 will be withdrawn from the study.

The following is the dosing schedule by weight for subjects who complete the antecedent study >15 days before the Screening Visit of this study:

Weight (kg)	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	≥60 and Adults
Dose 1 (mg/day)[a,b]	80	120	120	120	160	160	160	200	200	200	200
Dose 2 (mg/day)[a,b]	160	200	240	240	280	280	320	360	360	360	400
Dose 3 (mg/day)[a,b]	220	260	320	360	400	440	480	480	520	560	600

[a] Soticlestat dosing will be calculated based on body weight in pediatric subjects only. Dose will be recalibrated approximately every 6 months at clinic visits during the Maintenance Period, to ensure that the dose is current weight–appropriate.
[b] Daily doses are divided equally and administered twice daily.

Subjects who complete double-blind antecedent studies ≤15 days before screening in this study will be managed as follows:

- 1-week Dose Optimization Period (see Dosing and Titration Schedule, below).
- Maintenance Period until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor.
- 4-week Safety Follow-up Period of soticlestat dose tapering (up to 2 weeks) and safety follow-up.

Subjects who complete the antecedent study ≤15 days before the Screening Visit of this study will not undergo the 4-week Baseline Period. These subjects may complete Visit 1 (Screening) and Visit 2 on the same day. At Visit 1, informed consent and/or assent (if applicable) is obtained from the subjects and/or subjects' legally acceptable representative. Subjects will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria. Identical assessments for subjects who complete the last visit of their antecedent protocol ≤30 days before the Screening Visit in this study do not need to be repeated. Subjects and/or subjects' caregivers will be provided with a seizure diary and will be instructed to record seizure data on a daily basis. For subjects in this group, the seizure diary data collected during the 4-week prospective Baseline Period of the antecedent study will be used as the baseline seizure data for endpoint analysis in this study. The seizure diary recording can begin as soon as the informed consent has been signed.

Dosing and Titration Schedule

Subjects will initiate the soticlestat at Dose 1 and the dose will be titrated up at Day 8 as shown in the table below. After up-titration, subjects who cannot tolerate the new dose may have their dose reduced, based on the investigator's judgment and in consultation with the subject's caregiver, when applicable. Subjects will be contacted by phone 2 days following escalation to the maximum dose to assess safety and tolerability of the study drug. Dosing may be adjusted at the investigator's discretion throughout the study; however, frequent adjustments are discouraged.

Adult subjects who cannot tolerate at least 100 mg BID dosing will be withdrawn from the study. Pediatric subjects who cannot tolerate Dose 1 will be withdrawn from the study.

The following is the dosing schedule by weight for subjects who complete double-blind antecedent studies ≤15 days before the Screening Visit of this study:

Weight (kg)	**10-14**	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**≥60 and Adults**
Dose 1 (mg/day)[a,b]	160	200	240	240	280	280	320	360	360	360	400
Dose 2 (mg/day)[a,b]	220	260	320	360	400	440	480	480	520	560	600

[a] Soticlestat dosing will be calculated based on body weight in pediatric subjects only. Dose will be recalibrated approximately every 6 months at clinic visits during the Maintenance Period, to ensure that the dose is current weight-appropriate.

[b] Daily doses are divided equally and administered twice daily.

Subjects who complete the open-label antecedent study ≤15 days before screening in this study (only) will be managed as follows:

- Maintenance Period until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor.
- 4-week Safety Follow-up Period of soticlestat dose tapering (up to 2 weeks) and safety follow-up.

Subjects who complete the open-label antecedent study ≤15 days before the Screening Visit of this study will not undergo the 4-week Baseline Period or the 2-week Dose Optimization Period. These subjects may complete Visit 1 (Screening) and Visit 2 (Day 1) on the same day. At Visit 1, informed consent and/or assent (if applicable) is obtained from the subjects and/or subjects' legally acceptable representative. Subjects will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria. Identical assessments for subjects who complete the last visit of their antecedent protocol ≤30 days before the Screening Visit in this study do not need to be repeated. Subjects and/or subjects' caregivers will be provided with a seizure diary and will be instructed to record seizure data on a daily basis. For subjects in this group, the seizure diary data collected during the 4-week prospective Baseline Period of the antecedent study will be used as the baseline seizure data for endpoint analysis in this study. The seizure diary recording can begin as soon as the informed consent has been signed.

Dose Tapering

During the tapering period of not more than 14 days, the soticlestat dose will be decreased to the next lower level no more frequently than every 3 days based on the investigator's discretion until soticlestat is discontinued. After tapering, subjects will complete a Safety Follow-up visit (Visit 11) approximately 15 days after the last dose of study drug and exit the study.

Assessments

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

Safety, efficacy, and exploratory assessments will be performed at scheduled visits throughout the treatment period. Adverse events and concomitant medications will be monitored continuously throughout the study.

Efficacy will be assessed by seizure frequency, derived from seizure data obtained from seizure diaries collected throughout the study.

Blood samples for hematology and serum chemistry assessments are scheduled for collection at Visit 1 (Screening), Visit 2 (Day 1), Visit 5 (Week 24), Visit 7 (Week 48), Visit 9 (Week 78), and every 6 months thereafter. [redacted]

Procedures:

Screening/baseline assessments and Visit 2 (Day 1) assessments may coincide with the final visit of the antecedent study.

Safety assessments will be conducted at every visit throughout the study.

- Information about AEs and concomitant medications will be collected at every visit.
- Neurological examinations and physical examinations will be conducted at every visit.
- Hematology and serum chemistry assessments are scheduled for Visit 1 (Screening), Visit 2 (Day 1), Visit 5 (Week 24), Visit 7 (Week 48), Visit 9 (Week 78), and every 6 months thereafter. [redacted]
- An electrocardiogram (ECG) evaluation will be conducted at Screening; Weeks 24, 48, and 78; and every 6 months thereafter.
- The Columbia-Suicide Severity Rating Scale will be completed at Screening; Day 1; Weeks 24, 48, and 78; and every 6 months thereafter.
- The Vineland Adaptive Behavior Scale and Aberrant Behavior Checklist-Community Edition questionnaire will be completed at Screening; Weeks 24, 48, and 78; and every 6 months thereafter.
- The Quality of Life in Childhood Epilepsy and Sleep Disruption Numerical Rating Scale will be assessed (in pediatric subjects) at Screening; Day 1; Weeks 24, 48, and 78; and every 6 months thereafter.
- Efficacy will be assessed with daily seizure diaries collected at every visit.

Primary Objectives:

To assess the long-term safety and tolerability of soticlestat when administered as adjunctive therapy in subjects with rare epilepsies.

Secondary Objectives:

The secondary objectives, in subjects receiving soticlestat as adjunctive therapy to antiseizure therapy, are the following:

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

Subject Population: Pediatric (ages ≥6 to <18 years) and adult subjects (≥18 years) with epilepsy who participated in an antecedent study of soticlestat.

Eligibility

Subjects who participated in a previous soticlestat study and meet one of the following conditions:

- Successfully completed a soticlestat clinical study.

- Received at least 10 weeks of treatment (combined Dose Optimization and Maintenance Period) with the study drug in a soticlestat clinical study and the subject did not have a serious or severe adverse event (AE) that, in the investigator's or sponsor's opinion, was related to the study drug and would make it unsafe for the subject to continue receiving the study drug.

Number of Subjects:	**Number of Sites:**
Approximately 160.	Estimated total: Approximately 70.
Dose Levels: Adult subjects: 100, 200, 300 mg BID Pediatric subjects: Weight-based equivalent dosing in subjects with body weight of <60 kg.	**Route of Administration:** Oral or via G-tube or PEG tube, or J-tube.
Duration of Treatment: Dose optimization period: 1 or 2 weeks Maintenance Period: until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor Tapering period: 2 weeks	**Period of Evaluation:** Screening/baseline period: Maximum of 4 weeks Dose optimization period: 1 or 2 weeks Maintenance Period: until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor. Tapering period: 2 weeks Safety follow-up period: 2 weeks

Main Criteria for Inclusion:

Subjects must have participated in a previous soticlestat study and meet one of the following conditions:

- Successfully completed a soticlestat clinical study.
- Received at least 10 weeks of treatment (combined Dose Optimization and Maintenance Period) with the study drug in a soticlestat clinical study and the subject did not have a serious or severe AE that, in the investigator's or sponsor's opinion, was related to the study drug and would make it unsafe for the subject to continue receiving the study drug.
- In the opinion of the investigator, the subject has the potential to benefit from the administration of soticlestat (not applicable for Spain).

Main Criteria for Exclusion:

- Clinically significant disease, that, in the investigator's opinion, precludes study participation.
- Suicide attempt within the last year, at significant risk of suicide (either in the opinion of the investigator or defined as 'yes' to suicidal ideation question 4 or 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS] at Screening) or appearing suicidal per investigator judgment.

Main Criteria for Evaluation and Analyses:

Primary Endpoints—Safety

- Incidence of AEs.
- Change from Baseline in behavioral and adaptive functional measures using the Vineland Adaptive Behavior Scale.
- Change from Baseline in behavior measures using total scores and subscale scores of the Aberrant Behavior Checklist-Community Edition for subjects ≥6 years of age.
- Change from Baseline in the Columbia-Suicide Severity Rating Scale categorization based on Columbia Classification Algorithm of Suicide Assessment categories 1, 2, 3, 4, and 5 for subjects ≥6 years of age.
- Absolute values and change from Baseline in clinical laboratory assessments, vital sign measurements, body weight, and ECG parameters.
- Incidence of potentially clinically significant clinical safety laboratory test values, vital signs, weight, height, and ECG evaluations.

Secondary Endpoints

- Percent change from Baseline in all seizure 28-day frequency.
- Percent change from Baseline in drop seizure 28-day frequency.
- Percent change from Baseline in convulsive seizure 28-day frequency.
- Percent change from Baseline in motor seizure 28-day frequency.
- Change from Baseline in CGI-S.

Statistical Considerations:

All statistical analyses will be performed using SAS® software (SAS Institute Inc, Cary, NC) Version 9.4 or higher. All clinical study data will be presented in subject data listings. Data summaries will be presented for all endpoints and will include descriptive statistics (number of subjects [n], mean, standard deviation [SD], first quartile [Q1], median, third quartile [Q3], minimum, and maximum) for continuous variables and frequency and percentage for categorical and ordinal variables. If there are missing values, the number of missing will be presented, but without a percentage.

Baseline for efficacy analyses is the baseline of the antecedent study, except for subjects who rolled over more than 15 days after completion of the antecedent study.

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

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

Safety Analysis Set

All enrolled subjects who take at least 1 dose of study medication in this study will be included in the safety analysis set. All analyses will be conducted using the safety analysis set, based on the treatment that was actually administered to each subject in the antecedent study. In addition, subject disposition, demographics, and baseline characteristics will be summarized using the safety analysis set.

Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints. Two-sided 95% confidence intervals (CIs) will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital sign measurements, body weight, body weight by age group, ECG parameters, as well as changes in behavioral and adaptive functioning measures using Vineland Adaptive Behavior Scale and subscales of Aberrant Behavior Checklist-Community Edition, as appropriate. Changes from Baseline to study timepoints in clinical chemistry and hematology results will be summarized descriptively. Each laboratory parameter will be classified as low, normal, or high relative to the parameter's reference range. The number and percentage of subjects with shifts in clinical laboratory parameters will be summarized. Laboratory abnormalities for each treatment will also be summarized with shift tables. Listings of subjects with abnormal results will be provided.

The number and percentage of subjects with Columbia-Suicide Severity Rating Scale assessments of suicidal ideation and behavior will also be summarized.

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

The following definitions will be used for AEs:

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

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

Prior and concomitant medication use will be summarized by World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification system. Listings will be provided for all concomitant medications.

Efficacy Analyses Descriptive statistics will be used to summarize all efficacy endpoints (seizure frequencies over a 28-day period and CGI-S). Two-sided 95% CIs will be presented where meaningful. Changes in drop, convulsive, and motor seizure frequency will be calculated and summarized.
Sample Size Justification: No formal sample size calculation has been performed for this extension study. Subjects from the phase 2 studies TAK-935-2001, TAK-935-2002 (ELEKTRA) and TAK-935-18-002 (ARCADE) have the opportunity to roll over to this OLE study; therefore, there is the potential to enroll approximately 160 subjects.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform these activities either in full or in partnership with the sponsor.

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

Term	Definition
24HC	24*S*-hydroxycholesterol
ABC-C	Aberrant Behavior Checklist-Community Edition
AE	adverse event
AED	antiepileptic drugs
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice a day
CDKL5	cyclin-dependent kinase-like 5
CH24H	cholesterol 24*S*-hydroxylase
CGI-S	Clinician's Clinical Global Impression of Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEE	developmental and epileptic encephalopathy
Dup15q	chromosome 15q duplication
DS	Dravet syndrome
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EE	epileptic encephalopathy
EO	enzyme occupancy
G-tube	gastrostomy tube
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDMC	independent Data Monitoring Committee
IEC	independent ethics committee
IRB	institutional review board
IWRS	interactive web response system
J-tube	jejunostomy tube
LGS	Lennox-Gastaut syndrome
OLE	open-label extension
PEG tube	percutaneous endoscopic gastrostomy tube
PET	positron emission tomography
PD	pharmacodynamic(s)

Term	Definition
PK	pharmacokinetic(s)
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SoA	schedule of assessments
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VABS	Vineland Adaptive Behavior Scale

4.0 INTRODUCTION

4.1 Background

Soticlestat (TAK-935) is a potent and selective cholesterol 24*S*-hydroxylase (CH24H) inhibitor currently in development for adjunct treatment of developmental and epileptic encephalopathies (DEEs).

In the brain, cholesterol is metabolized by CH24H, which is specifically and constitutively expressed in neurons, to 24*S*-hydroxycholesterol (24HC). This cholesterol metabolite, 24HC, leaves the brain via lipoproteins and is excreted in bile. Aberrant cholesterol metabolism is implicated in epilepsy disorders and syndromes.

Under normal conditions, extracellular glutamate is sequestered by glutamate transporters on neighboring astrocytes that require adequate cholesterol levels to efficiently maintain lipid raft structures in the astrocyte plasma membrane. Upon central nervous system injury, CH24H is induced in reactive astrocytes and microglia. This leads to disruption in astrocytic glutamate homeostasis and a large increase in extracellular glutamate levels. As CH24H converts cholesterol essential for the integrity of plasma membrane lipid rafts to 24HC, the circulating levels of 24HC increase and may further contribute to underlying pathophysiological processes. Excessive extracellular glutamate and 24HC levels are thought to play major roles in excitotoxicity either through a sustained activation of the N-methyl-D-aspartate receptor channel or as a positive allosteric modulator of the receptor [1]. The processes may be equally important in contributing to the enhanced glutamatergic activity observed in epilepsy disorders.

At the time of the initial protocol, soticlestat had been studied in 4 completed phase 1 clinical studies: a single-rising dose first-in-human study, a single-dose positron emission tomography (PET) target occupancy study (PET study), a multiple-rising dose study, and a single-dose relative bioavailability and food-effect study. The pharmacokinetics (PK) and pharmacodynamics (PD) of soticlestat in healthy subjects were characterized in these studies. In addition, the PET study provided clinical evidence of dose-dependent decreases in plasma 24HC concentrations and PET occupancy measurements that were dose- and time-dependent and correlated with circulating levels of 24HC. A phase 1b/2a study (TAK-935-2001) in 18 adults with DEE had recently completed (Section 4.2). In addition, to date, the following additional clinical studies have been completed: a phase 1, single- and multiple- rising dose study in Japanese subjects (TAK-935-1004); a phase 2 study in pediatric subjects with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) (TAK-935-2002); and a phase 2 study in pediatric subjects with chromosome 15q duplication (Dup 15q) and cyclin-dependent kinase-like 5 (CDKL5) deficiency syndromes (TAK-935-18-002) (Section 4.2).

More information about these studies and the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of soticlestat may be found in the current edition of the investigator's brochure (IB).

4.2 Study Rationale

Epileptic encephalopathies (EEs) are a group of rare disorders in which unremitting epileptic activity contributes to severe cognitive and behavioral impairment that can worsen over time and lead to progressive cerebral dysfunction [2]. Epileptic encephalopathies typically start at an early age and manifest with seizures that are usually intractable, with electroencephalogram paroxysmal abnormalities. Severe neurocognitive deficits are commonly found in EEs, which may be susceptible to a common treatment. In a group of severe genetic disorders causing EE, the underlying genetic mutation also contributes to developmental delay. Hence, the International League Against Epilepsy expanded the concept of EE from the severe epilepsies with onset in infancy and childhood to epilepsy syndromes associated with encephalopathy that have a genetic etiology [3]. The revised classification now refers to DEEs.

Based on the efficacy, safety, and tolerability data collected in the phase 2 ELEKTRA study, combined with the safety and tolerability data from phase 1 and other completed or ongoing studies (please see the current IB), soticlestat is being evaluated as adjunctive therapy in pediatric and adult subjects with DS or LGS, highly impacted populations with great unmet need.

This OLE study is designed to obtain additional safety, tolerability, efficacy, [redacted] data related to soticlestat administered long-term in subjects who participated in either of the phase 1b/2a or phase 2 clinical studies noted above.

5.0 STUDY OBJECTIVES AND ENDPOINTS

Study objectives and associated endpoints are presented in Section 5.1 and Section 5.2, respectively; the frequency and timing of study measurements is provided in the Schedule of Assessments (Appendix A).

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 Secondary Objectives

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

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

5.1.3 Exploratory Objective

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

- To assess the quality of life.
- To assess sleep disruption.

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints - Safety

The primary endpoints (safety) include the following:

- Incidence of AEs.
- Change from Baseline in behavioral and adaptive functional measures using the Vineland Adaptive Behavior Scale (VABS).
- Change from Baseline in behavior measures using total scores and subscale scores of the Aberrant Behavior Checklist-Community Edition (ABC-C) for subjects ≥6 years of age.
- Change from Baseline in the Columbia-Suicide Severity Rating Scale (C-SSRS) categorization based on Columbia Classification Algorithm of Suicide Assessment categories 1, 2, 3, 4, and 5 for subjects ≥6 years of age.
- Absolute values and change from Baseline in clinical laboratory assessments, vital sign measurements, body weight, and electrocardiogram (ECG) parameters.
- Incidence of potentially clinically significant clinical safety laboratory test values, vital signs, weight, height, and ECG evaluations.

5.2.2 Secondary Endpoints

The secondary endpoints (efficacy) include the following:

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

5.2.3 Exploratory Endpoints

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

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Summary of Study Design

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

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

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

Approximately 160 subjects from several antecedent studies will be rolled over into this study. Study design, including timing of enrollment and dosing and titration schedule, is presented in Section 8.2.

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

The Schedule of Study Procedures is presented by visit in Appendix A and study procedures are presented in detail in Section 9.0. The Screening/Baseline visit may occur on the same day as the end of treatment visit of the antecedent study or within 30 days after the end of treatment visit of the antecedent study. Identical assessments taken at the subject's last visit of the antecedent

study do not need to be repeated at Visit 1 of this study if these 2 visits are ≤30 days apart. After Visit 1, subsequent visits will occur at Weeks 1 (Day 1), 4, 12, 24, 36, 48 (all in Year 1); every 13 weeks starting with Week 65 in Years 2 and 3; and every 26 weeks thereafter.

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

6.2 End of Study Definition

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

6.3 Dosing Rationale

All subjects will receive soticlestat. The planned doses of soticlestat represent the intended therapeutic doses of soticlestat and include the full range of doses available for soticlestat. Subjects will be titrated up to the maximum dose based on weight (see Sections 8.2.1 and 8.2.2).

Safety results from phase 1 studies in healthy subjects suggested that soticlestat up to a single dose of 1350 mg and multiple doses of soticlestat up to 400 mg once daily for 14 days is generally safe and well-tolerated. soticlestat has been evaluated at doses up to 600 mg once a day as well as 300 mg BID in healthy adult subjects in the multiple-rising dose study. When soticlestat was administered without titration, AEs that were considered by the investigator to be nonserious were observed in individual subjects at 300 mg BID (mental confusion of mild intensity) and 600 mg once daily (QD) (acute psychosis of severe intensity) dosing.

A population PK model for soticlestat has been developed using the data from 4 phase 1 studies in 104 subjects (1727 observations). For one of these studies, a selective PET ligand was developed and used to assess the central nervous system target engagement of soticlestat in healthy adult subjects (TAK-935-1003), and when combined with data from 3 other phase 1 studies, a preliminary PK/PD/enzyme occupancy (EO) model was developed [4]. This PK/PD/EO model was used to recommend the doses for the pediatric study. Model-based simulations were performed using allometric scaling on clearance and central volume of distribution for both QD and BID dosing regimens.

[redacted] The doses allowed were 20 mg or a multiple of 20 mg, with weight bins of 5 kg for subjects between 10 to 60 kg. The doses allowed were 100 mg or a multiple of 100 mg for subjects weighing ≥60 kg and adults.

In this OLE study, pediatric and adult subjects whose antecedent study was an open-label study will be started on the same soticlestat dose that they had maintained at the end of the antecedent study. For pediatric and adult subjects whose antecedent study was a blinded study, soticlestat

will be titrated as described in Section 8.2. This study will investigate long-term safety, tolerability, and effects on seizure frequency and quality of life of soticlestat in subjects who are also being treated with AEDs.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened up to 2 times, after approval by the medical monitor. Refer to Section 9.2 for additional information on recording screen failures.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

7.1 Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all the following criteria and none of the exclusion criteria (Section 7.2):

1. Subjects must have participated in a previous soticlestat study and meet one of the following conditions:
   - Successfully completed a soticlestat clinical study.
   - Received at least 10 weeks of treatment (combined Dose Optimization and Maintenance Period) with the study drug in an antecedent placebo-controlled blinded soticlestat clinical study and the subject did not have a serious or severe AE that, in the investigator's or sponsor's opinion, was related to the study drug and would make it unsafe for the subject to continue receiving the study drug.
2. In the opinion of the investigator, the subject has the potential to benefit from the administration of soticlestat (not applicable for Spain).
3. The subject provides written informed consent, or the subject's legal representative (ie, parent or legal guardian) provides written informed consent and the subject provides assent, before any study procedures are performed.
4. The subject and subject's legal representative (ie, parent or legal guardian) (as applicable) are willing to comply with all study requirements.
5. From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, female patients of childbearing potential* who are sexually active with a non-sterilized male partner** must agree to use a highly effective method of contraception (from the list below). In addition, they must not donate ova during this period.

   *Females NOT of childbearing potential are defined as those who are prior to first menarche or who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as ≥1 year since last regular menses with a follicle-stimulating hormone level >40 IU/L or ≥5 years since last regular menses, confirmed before any study drug is administered).

**Sterilized males should be ≥1 year post-vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

A highly effective method of contraception is defined as one that has no higher than a 1% failure rate per year when used consistently and correctly. In this study, the only acceptable methods of contraception are as follows:

a) Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   - Oral.
   - Intravaginal.
   - Transdermal.

b) Progestogen-only hormonal contraception associated with inhibition of ovulation:
   - Oral.
   - Injectable.
   - Implantable.

c) Double-barrier methods (each time the patient has intercourse):
   - Sponge (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.
   - Cap (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.
   - Diaphragm (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.

d) Intrauterine device (Copper T PLUS condom).

e) Intrauterine hormone-releasing system.

f) Sterilization:
   - Bilateral tubal occlusion.
   - Vasectomized partner (provided that the partner is the sole sexual partner of the patient and the absence of sperm in the ejaculate has been confirmed).

g) Sexual abstinence, if it is the preferred and usual lifestyle of the patient, will be considered an acceptable method of contraception on a case-by-case basis upon prior approval by the medical monitor. Patients practicing abstinence as a method of contraception must refrain from heterosexual intercourse throughout the duration of the study and for 30 days after last dose of study drug.

   From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, male patients (post-pubertal unless permanently

sterilized**) who are sexually active with a female partner of childbearing potential* must agree to use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must not donate sperm during this period.

7.2 Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria:

1. Clinically significant disease, that, in the investigator's opinion, precludes study participation.
2. Enrollment in any other clinical trial involving an investigational drug, device, or treatment in the past 90 days (with the exception of an antecedent study involving soticlestat).
3. Subject is currently pregnant or breastfeeding or is planning to become pregnant during the study or within 30 days of the last study drug administration.
4. Suicide attempt within the last year, at significant risk of suicide (either in the opinion of the investigator or defined as 'yes' to suicidal ideation question 4 or 5 on the C-SSRS at Screening) or appearing suicidal per investigator judgment.

7.3 Concomitant Medications

Use of strong inducers and inhibitors of cytochrome P450 (CYP)3A4 are prohibited, except for AEDs (eg, carbamazepine, phenobarbital, phenytoin). Refer to Appendix B for examples of prohibited CYP3A4 inducers and inhibitors.

Vaccinations are allowed; however, the medical monitor should be informed about changes in the subject's vaccination status.

Use of traditional Chinese medicines should be approved by the medical monitor at screening.

All medication including vitamin supplements, over-the-counter medications, and herbal preparations including (medical) marijuana and cannabidiol products will be collected throughout the study.

7.4 Discontinuations

7.4.1 Criteria for Discontinuation or Withdrawal of a Subject

The criteria for enrollment must be followed explicitly. If the investigative site identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified immediately. If the sponsor identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified immediately. A discussion must occur between the sponsor and the investigator to determine whether the subject may continue in the study, with or without study drug. Inadvertently enrolled subjects may be maintained in the study and on study drug when the sponsor agrees with the investigator that it is medically appropriate for that subject. The subject may not continue in the study with or without study drug if the sponsor does not agree with the investigator's determination that it is medically

appropriate for the subject to continue. The investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled subject to continue in the study with or without study drug.

In addition, patients will be discontinued from the study drug (and/or from the study) in the following circumstances:

- Liver function test abnormalities

  Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status, see Section 10.4.1), if the following circumstances occur at any time during study drug treatment:

  – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or

  – ALT or AST >5 × ULN and persists for >2 weeks, or

  – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio >1.5, or

  – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

- A corrected QT interval by Fridericia's formula (QTcF) >500 ms or an increase of QTcF >60 msec above baseline confirmed (persistent for at least 5 minutes) and determined postdose either during continuous 12-lead ECG monitoring or on a repeat 12-lead ECG. Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat ECG).

- Greater than a 100% increase in 28-day seizure frequency from the 4-week prospective Baseline Period (see formula in Section 9.1.8) and considered by the investigator to be clinically significant worsening of the seizure frequency. For subjects who do not undergo the Baseline Period in this study, the seizure frequency from the Baseline Period of the antecedent study will be used.

- Not tolerating the lowest dose of the titration schedule.

- Enrollment in any other clinical study involving a study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

- Suicidal ideation:

  – Study staff trained in the administration of the C-SSRS will assess subject suicidality using the C-SSRS (see Section 9.1.14), eliciting answers from the subject or the subject's caregiver. Subjects who experience suicidal ideation or attempt suicide will be immediately withdrawn from the study.

- Investigator decision (physician decision):
  - The investigator decides that the subject should be discontinued from the study; for example, if the subject is not responding to the treatment.
- Subject decision (withdrawal by subject or withdrawal by subject's legal representative [parent or legal guardian]):
  - The subject or the subject's legal representative (ie, parent or legal guardian) requests to be withdrawn from the study. The specific reason for discontinuation should be recorded in the electronic case report forms (eCRFs) and is only to be used if no other pertinent reason for discontinuation is applicable). All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in this category. Similarly, lack of efficacy should not be recorded in this category.
- Sponsor decision:
  - The sponsor or its designee discontinues the study or discontinues the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).
  - The sponsor or its designee stops the clinical study at a particular site.
- Adverse event:
  - If the investigator decides that the patient should be withdrawn because of a serious adverse event (SAE) or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The sponsor or its designee is to be alerted immediately (refer to Section 10.2).
- Lost to follow-up: The subject did not attend visits (clinical or virtual), and multiple attempts to contact the subjects were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
- Other: The specific reason should be recorded in the eCRF.
- Coronavirus disease 2019 (COVID-19)/pandemic: If, in the opinion of the investigator, the safety of a study subject is at risk because the subject cannot complete key evaluations or adhere to critical mitigation steps, then the investigator should consider discontinuing that subject. In addition, for any such subject with COVID-19 diagnosis or in a pandemic circumstance, GCP for AE reporting processes will apply.
- Significant noncompliance with study drug (as described in Section 8.4).
- Lack of efficacy.

Subjects who discontinue the study drug and/or study early will have end-of-study procedures/early termination visit performed as shown in the schedule of assessments (Appendix A).

7.4.2 Discontinuation of Study Sites/Site Terminated by Sponsor

Study site participation may be discontinued if the sponsor or its designee, the investigator, or the institutional review board/independent ethics committee (IRB/IEC) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

7.4.3 Discontinuation of the Study/Study Terminated by Sponsor

The study will be discontinued if the sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Materials and Supplies

The sponsor will supply the study sites with 100 mg soticlestat tablets and 20 mg soticlestat mini-tablets. Each bottle will contain a label that includes pertinent study information and caution statements.

Clinical study materials will be labeled according to each country's regulatory requirements.

If a subject is unable to come for a clinic visit to obtain study drug, the study drug may be shipped via a courier service.

8.1.1 Storage

Soticlestat tablets/mini-tablets are packaged in high-density polyethylene bottles with induction seals and child-resistant caps. Study drug must be kept in an appropriate, limited-access, secure place until it is dispensed or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day. Please refer to the pharmacy manual for additional information related to the study drug. In instances where the protocol and pharmacy manual text conflict, the pharmacy manual text shall supersede the text in the protocol.

8.2 Treatments Administered and Assignment to Treatment

All subjects will receive soticlestat BID, with or without food, orally or via G-tube or PEG tube. A J-tube may be considered following approval by the sponsor and medical monitor. Subjects enrolled in clinical sites in China are not to receive study drug via G-tube, PEG tube, or J-tube. No subject will receive placebo treatment in this OLE study. The planned doses of soticlestat represent the intended therapeutic doses of soticlestat and include the full range of doses available for soticlestat. Subjects will be titrated up to the maximum dose based on weight (see Sections 8.2.1 and 8.2.2). The maximum dose available for this study will be 600 mg/day (300 mg BID).

Tablets/mini-tablets may be crushed and mixed well in applesauce or thick liquid, for taste masking, prior to dosing. The amount of applesauce or liquid needed is dependent upon the number of tablets/mini-tablets the subject is taking. One-half teaspoon or 2.5 mL of applesauce or thick liquid is needed for each mini-tablet taken and 2 teaspoons or 10 mL, respectively, is needed for each tablet taken.

For subjects receiving study drug via G-tube or PEG tube (or J-tube if approved by the sponsor and medical monitor), tablets/mini-tablets will be crushed, suspended in water, and the suspension will be administered via the G-tube, PEG tube, or J-tube. Complete instructions will be provided to subjects/caregivers in a document provided outside of the protocol. Other medications or enteral feeds should not be given concurrently with soticlestat. Subjects enrolled in clinical sites in China are not to receive study drug via G-tube, PEG tube, or J-tube.

If a subject misses a dose, the missed dose should be skipped, and the subject should continue with his/her normal dosing schedule. The scheduled dose can be administered or taken up to 4 hours after the scheduled time of dosing. If the subject/caregiver remembers after 4 hours of the scheduled time of dosing, the dosing should be skipped and reported as a missed dose in their seizure diary and on the next clinic visit.

Subjects from 3 phase 1b/2a and phase 2 antecedent studies may be rolled over into this study. Subjects will be eligible for screening within 15 days of completing the last visit of the antecedent soticlestat study (except for adult subjects enrolled in the TAK-935-2001 study, who will be eligible for screening in this OLE study up to 15 months after completion of the antecedent study). A subject who completes the antecedent study between approximately 15 and 30 days before the Screening Visit of this OLE study may be entered in this study with the approval of the sponsor after considering the subject's overall compliance in the antecedent study and after the subject meets all inclusion and no exclusion criteria for this study.

Study design, including timing of enrollment and dosing and titration schedule, is based upon the age of the subject (pediatric or adult), the type of antecedent study completed (blinded or unblinded), and how many days elapsed between completing the antecedent study and the Screening Visit in this study (≤15 days or >15 days). In this OLE study, adults are defined as subjects who are 18 years or older.

8.2.1 Subjects Who Complete Antecedent Studies >15 Days Before Screening in This Study

Subjects who complete an antecedent study >15 days before screening in this study will be managed as follows:

- 4-week Screening/Baseline Period.
- 2-week Dose Optimization Period (Table 8.a).
- Maintenance Period until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor.

- 4-week Safety Follow-up Period of soticlestat dose tapering (up to 2 weeks) and safety follow-up.

At the Screening Visit (Visit 1), informed consent and/or assent (if applicable) is obtained from the subjects and/or subjects' legally acceptable representative. Subjects will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria. Identical assessments for subjects who complete the last visit of their antecedent protocol ≤30 days before the Screening Visit in this study do not need to be repeated. At this Screening Visit and at subsequent visits, subjects and/or subjects' caregivers will be provided with a seizure diary and will be instructed to record seizure data on a daily basis. The seizure diary data collected during the 4-week Baseline Period will be used as the baseline for endpoint analysis in this study. The 4-week Baseline Period seizure diary recording can begin the day after informed consent has been signed. At the end of the 4-week Baseline Period, subjects will return to the clinic on Visit 2 (Day 1).

Dosing and Titration Schedule

Subjects will initiate the soticlestat at Dose 1, and the dose will be titrated up every 7 days (Day 8 and Day 15) as shown in Table 8.a. Two days after each change in dose, subjects will be contacted by phone to monitor study drug compliance, concomitant medication use, and AEs. Subjects who cannot tolerate Dose 1 will be withdrawn from the study. After up-titration, subjects who cannot tolerate the new dose may have their dose reduced, based on the investigator's judgment and in consultation with the subject's caregiver, when applicable. Subjects will be contacted by phone 2 days following escalation to the maximum dose to assess safety and tolerability of the study drug. Dosing may be adjusted at the investigator's discretion throughout the study; however, frequent adjustments are discouraged.

Adult subjects who cannot tolerate at least 100 mg BID dosing will be withdrawn from the study. Pediatric subjects who cannot tolerate Dose 1 will be withdrawn from the study.

Table 8.a Dosing Schedule by Weight for Subjects Who Complete the Antecedent Study >15 Days Before the Screening Visit of This Study

Weight (kg)	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	≥60 and Adults
Dose 1 (mg/day)[a,b]	80	120	120	120	160	160	160	200	200	200	200
Dose 2 (mg/day)[a,b]	160	200	240	240	280	280	320	360	360	360	400
Dose 3 (mg/day)[a,b]	220	260	320	360	400	440	480	480	520	560	600

[a] Soticlestat dosing will be calculated based on body weight in pediatric subjects only. Dose will be recalibrated approximately every 6 months at clinic visits during the Maintenance Period, to ensure that the dose is current weight-appropriate.

[b] Daily doses are divided equally and administered twice daily.

8.2.2 Subjects Who Complete Double-blind Antecedent Studies ≤15 Days Before Screening in This Study

Subjects who complete a double-blind antecedent study ≤15 days before screening in this study will be managed as follows:

- 1-week Dose Optimization Period (Table 8.b).
- Maintenance Period until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor.
- 4-week Safety Follow-up Period of soticlestat dose tapering (up to 2 weeks) and safety follow-up.

Subjects who complete the antecedent study ≤15 days before the Screening Visit of this study will not undergo the 4-week Baseline Period. These subjects may complete Visit 1 (Screening) and Visit 2 on the same day. At Visit 1, informed consent and/or assent (if applicable) is obtained from the subjects and/or subjects' legally acceptable representative. Subjects will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria. Identical assessments for subjects who complete the last visit of their antecedent protocol ≤30 days before the Screening Visit in this study do not need to be repeated. Subjects and/or subjects' caregivers will be provided with a seizure diary and will be instructed to record seizure data on a daily basis. For subjects in this group, the seizure diary data collected during the 4-week prospective Baseline Period of the antecedent study will be used as the baseline seizure data for endpoint analysis in this study. The seizure diary recording can begin as soon as the informed consent has been signed.

Dosing and Titration Schedule

Subjects will initiate the soticlestat at Dose 1 and the dose will be titrated up at Day 8 as shown in Table 8.b. After up-titration, subjects who cannot tolerate the new dose may have their dose reduced, based on the investigator's judgment and in consultation with the subject's caregiver, when applicable. Subjects will be contacted by phone 2 days following escalation to the maximum dose to assess safety and tolerability of the study drug. Dosing may be adjusted at the investigator's discretion throughout the study; however, frequent adjustments are discouraged.

Adult subjects who cannot tolerate at least 100 mg BID dosing will be withdrawn from the study. Pediatric subjects who cannot tolerate Dose 1 will be withdrawn from the study.

Table 8.b Dosing Schedule by Weight for Subjects Who Complete the Double-blind Antecedent Study ≤15 Days Before the Screening Visit of This Study

Weight (kg)	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	≥60 and Adults
Dose 1 (mg/day)[a,b]	160	200	240	240	280	280	320	360	360	360	400
Dose 2 (mg/day)[a,b]	220	260	320	360	400	440	480	480	520	560	600

[a] Soticlestat dosing will be calculated based on body weight in pediatric subjects only. Dose will be recalibrated approximately every 6 months at clinic visits during the Maintenance Period, to ensure that the dose is current weight-appropriate.
[b] Daily doses are divided equally and administered twice daily.

8.2.3 Subjects Who Complete the Open-Label Antecedent Study ≤15 Days Before Screening in This Study (Only)

Subjects who complete the open-label antecedent study ≤15 days before screening in this study (only) will be managed as follows:

- Maintenance Period until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor.
- 4-week Safety Follow-up Period of soticlestat dose tapering (up to 2 weeks) and safety follow-up.

Subjects who complete the open-label antecedent study ≤15 days before the Screening Visit of this study will not undergo the 4-week Baseline Period or the 2-week Dose Optimization Period. These subjects may complete Visit 1 (Screening) and Visit 2 (Day 1) on the same day. At Visit 1, informed consent and/or assent (if applicable) is obtained from the subjects and/or subjects' legally acceptable representative. Subjects will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria. Identical assessments for subjects who complete the last visit of their antecedent protocol ≤30 days before the Screening Visit in this study do not need to be repeated. Subjects and/or subjects' caregivers will be provided with a seizure diary and will be instructed to record seizure data on a daily basis. For subjects in this group, the seizure diary data collected during the 4-week prospective Baseline Period of the antecedent study will be used as the baseline seizure data for endpoint analysis in this study. The seizure diary recording can begin as soon as the informed consent has been signed.

Dosing and Titration Schedule

Pediatric and adult subjects whose antecedent study was an open-label study will be started on the same soticlestat dose that they had maintained at the end of the antecedent study. Dosing may be adjusted at the investigator's discretion throughout the study; however, frequent adjustments are discouraged. Dosing will be calculated based on body weight in pediatric subjects only. Dose

will be recalibrated approximately every 6 months at clinic visits during the Maintenance Period, to ensure that the dose used is weight-appropriate.

8.2.4 Dose Tapering

During the tapering period of not more than 14 days following the final maintenance visit, the soticlestat dose will be decreased to the next lower level no more frequently than every 3 days based on the investigator's discretion until soticlestat is discontinued. After tapering, subjects will complete a Safety Follow-up visit approximately 15 days after the last dose of study drug and exit the study.

8.2.5 Investigator Responsibilities for Drug Administration

The investigator or his/her designee is responsible for the following:

- Explaining the correct use of the investigational agent(s) to the subject/site personnel/legal representative.
- Verifying that instructions are followed properly.
- Maintaining accurate records of study drug dispensing and collection.
- Returning or destroying all unused medication to the sponsor or its designee at the end of the study.

In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical study materials.

Subjects or the subject's legal representative (ie, parent or legal guardian) will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

All clinical trial material provided to the investigator will be stored in a secure and locked place and allocated and dispensed by qualified personnel and through interactive web response system (IWRS). Detailed records of the amounts of the study drug received, dispensed, and remaining at the end of the study will be maintained.

Soticlestat tablets/mini-tablets will be administered orally or via G-tube, PEG tube, or J-tube at approximately the same times on each day. The actual times of all dose administrations [redacted] will be recorded in each subject's source documents and transcribed into eCRFs.

8.3 Blinding

This is an open-label study. There will be no blinding.

8.4 Treatment Compliance

Subject compliance with study medication will be assessed at each visit. Subjects and/or subjects' caregivers will be required to bring study drug bottles/unused study drug to each dispensing site visit. The date and time of each dose will be recorded in the source documents and in the eCRFs. All subjects and/or subjects' caregivers should be re-instructed about the dosing requirements during study visits. The authorized study personnel conducting the re-education must document the process in the subject source records.

Subjects who are significantly noncompliant will be discontinued from the study. A subject will be considered significantly noncompliant if he or she intentionally misses more than 20% of study medication between any 2 visits during the study. Similarly, a subject will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures to be performed and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Study procedures and their timing are summarized in the Schedule of Study Procedures (Appendix A).

9.1.1 COVID-19 Pandemic Study Procedures

Please see Appendix C.

9.1.2 Informed Consent Procedures

Remote consenting is allowed for subjects rolling over to ENDYMION 1 from an antecedent soticlestat trial. Consent can be performed in the manner approved by the Institutional Review Board or Ethics Committee (eg, video, phone, telehealth/telemedicine, email, and/or mail). A signed document is required (either wet or electronic signature) before study drug can be dispensed.

Two copies of the Informed Consent Form (ICF) will be sent to the subject's home via courier and/or emailed to the subject/subject's caregiver in advance of the planned screening visit date. Mailing/courier materials needed for returning 1 original copy of the signed consent form will be provided to the subject/caregiver if a wet signature is used.

On the agreed upon consent date, the investigator or a delegated member of the site staff will contact the subject/subject's caregiver via video, phone, or telehealth/telemedicine utilized by the institution, outline the study procedures within the consent form, discuss any questions from subject/subject's caregiver, and obtain verbal consent and ultimately, written and signed. Conduct of this process will be documented in the source documents by the site staff.

Please ensure the following is documented in the source document but not limited to the following:

- The date and time of the consent discussion.
- Method of conducting consent discussion (video, phone, or telehealth/telemedicine).
- Name and relationship of individuals who were present during the consent discussion.
- Name and relationship of individuals who signed the consent.
- Responses to any questions asked by the subject and/or caregiver.
- Confirmation that the subject/caregiver questions were adequately answered.
- Confirmation by the Investigator or delegated staff member that the subject/caregiver is willing to participate in the study and signed the consent during the discussion.
- Verbal confirmation from the subject/caregiver that they wish to participate in the trial and have signed and dated the consent form in their possession.
- Method by which the signed consent will be provided to the site (ie email, postal mail/courier, or in person at next on-site visit).

Once all questions regarding study participation are answered and verbal consent is obtained, the subject/caregiver will sign and date the consent form. If possible, a scanned copy of the signed consent form should be emailed to the site as evidence of the consent agreement prior to study drug dispensation. In addition, one of the original signed consent forms must be provided to the site using the provided shipping/courier supplies (if this is not possible, the original signed consent form should be brought to the site at the time of the next on-site visit).

The investigator or delegated staff will sign and date a copy of the consent form and mail or email a copy to the subject/caregiver.

Original copies of the signed consent forms will be maintained by the site.

9.1.2.1 Materials and Supplies

To ensure the safe and continued study participation, once verbal consent from the subject/caregiver is received, sites will arrange for delivery of intellectual property, paper copies of applicable scales, and the seizure and dosing diary to the subject's home via courier. Administration of the ENDYMION 1 study drug should begin according to the Day 1 procedures indicated in Appendix A.

9.1.2.2 Screening/Baseline Visit

Ensure remote consent processes are in place to allow rollover from antecedent soticlestat study without an on-site subject visit. Consent can be done by video, phone, telehealth/telemedicine, and/or mail. A signed document is required (either wet or electronic signature) before study drug can be assigned or dispensed. Mailed/emailed study documents should be sent to the subject

prior to the phone visit. Investigational Product, applicable scales and seizure and dosing diaries will be delivered to the subject's home via courier.

9.1.3 Demographics, Medical History, and Medication History Procedures

Demographic information may be collected via video, phone, or telehealth/telemedicine by site staff.

Demographic information to be obtained will include year of birth, gender, ethnicity, and race as described by the subject/caregiver.

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. Medical and medication history data from antecedent studies may be carried over and recorded in the eCRFs in this study if these data are available; otherwise, new medical and medication history data should be collected at the screening of this study. For subjects with ongoing AEs in the antecedent study, their ongoing AEs should be recorded as medical history in this OLE study.

9.1.4 Physical Examination Procedure

Physical examinations may be conducted via video, phone, or telehealth/telemedicine by site staff or locally by Health Care Practitioners (HCP) or Primary Care Physicians (PCP).

The physical examination will consist of the following body systems: (1) head, eyes, ears, nose, and throat; (2) cardiovascular system; (3) respiratory system; (4) gastrointestinal system; (5) dermatologic system; (6) extremities; (7) musculoskeletal system; (8) lymph nodes; (9) psychiatric status; and (10) other. The physical examination must be captured in the source document and eCRF.

9.1.5 Neurological Examination Procedure

Neurological examinations may be conducted via video, phone, telehealth/telemedicine by site staff or locally by HCP or PCP.

A separate neurological examination will be performed and collected in the eCRF. This will include testing mental status, gait, cerebellar function, cranial nerves, motor function, and sensation.

As part of the neurological exam, vision testing should include fundoscopy (including examination of the optic disc), best corrected visual acuity using a pocket vision screening card or wall card, and visual field assessment. If this is not possible to perform, justification should be provided.

9.1.6 Height and Weight

Height and weight data may be obtained locally by HCP or PCP.

Height and weight are to be measured while the subject is wearing indoor clothing and with shoes off. If unable to obtain height or weight, data may be collected from other sources (eg, medical records or the subject's caretaker). The investigator must document in the source document the reason for not obtaining height or weight (eg, the subject is in a wheelchair).

9.1.7 Vital Signs Measurements

Vital signs data may be obtained locally by HCP or PCP.

Vital signs to be measured are temperature, blood pressure, heart rate (beats per minute), and respiratory rate.

Vital signs should be measured at the same time of day across visits, if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 15 minutes before or after the scheduled blood draw, if possible.

All vital signs data collected at study visits will be recorded on the source documents and in the eCRF.

9.1.8 Seizure and Dosing Diary Procedure

At Visit 1 and at every subsequent clinic visit, the subject and/or subject's caregiver will be sent a seizure and dosing diary via courier and specific instructions to ensure compliance with the seizure and study drug recording. The seizure events will be recorded starting at the Screening/Baseline Period up until the Follow-up Visit. In preparation for each remote clinic visit, the seizure and dosing diary will be collected from the subject's home either via courier or sent electronically to the site by the subject and/or subject's caregiver for review. Seizure diaries may be returned via courier as frequently as every month for convenience of the subject and/or subject's caregiver and the site. The PI will continue to review with the subject and/or subject's caregiver for proper recording and accountability via video, phone, telehealth/telemedicine.

The 28-day seizure frequency will be calculated from the seizure diary using the following formula:

(# of seizures) / (# of days seizures were assessed) × 28

9.1.9 Documentation of Concomitant Medications

Concomitant medications may be collected via telehealth/telemedicine video, phone, telehealth/telemedicine by site staff. Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or they may be over-the-counter medications. At the time of each study visit, subjects and/or caregivers will be asked whether subjects have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and herbal preparations including (medical) marijuana and cannabidiol products, must be recorded in the source document and eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.10 Documentation of Concurrent Medical Conditions

Concurrent medical conditions may be collected via video, phone, telehealth/telemedicine by site staff.

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 judgment of the investigator. The condition (ie, diagnosis) should be described and recorded on the Medical History form.

9.1.11 Procedures for Clinical Laboratory Samples

Clinical laboratory samples may be collected and analyzed by a local laboratory at the investigator's discretion with results sent to the clinical site.

Blood samples are to be collected at the time points stipulated in the Schedule of Study Procedures (Appendix A). Samples will be collected in accordance with local laboratory procedures.

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and specimen handling will be given in the laboratory manual. The approximate volume of blood collected at any single visit and the approximate total volume of blood collected in the study will be given in the laboratory and/or study manual.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Serum (Concomitant AEDs) [a]
RBC	ALT	Carbamazepine
WBC with differential (% and absolute)	Albumin	Clobazam
	Alkaline phosphatase	N-Desmethylclobazam
Hemoglobin	AST	Valproic acid
Hematocrit	Total bilirubin	Phenytoin
Platelets	Total protein	Topiramate
	Creatinine	Lamotrigine
	Blood urea nitrogen	Rufinamide
	Creatine kinase	Zonisamide
	GGT	Phenobarbital
	Potassium	Levetiracetam
	Sodium	Lacosamide
	Glucose	10-hydroxycabazepine (metabolite of oxcarbazepine)
	Chloride	Oxcarbazepine
	Bicarbonate	Cannabidiol (CBD)
	Calcium	
	Total cholesterol	
	HDL cholesterol	
	LDL cholesterol	
	Triglycerides	

Other:
Human chorionic gonadotropin (for pregnancy) [b]

AED: antiepileptic drug; ALT: alanine aminotransferase AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; hCG human chorionic gonadotropin: HDL: high-density lipoprotein; LDL: low-density lipoprotein RBC: red blood cell; WBC: white blood cell.
[a] As applicable, at investigator discretion.
[b] Only for sexually active female patients of childbearing potential. An additional serum hCG pregnancy test will be performed at the final maintenance visit. Additional pregnancy tests (urine only) may be performed throughout the study at the investigator's discretion.

9.1.12 Contraception and Pregnancy Avoidance Procedure

Pregnancy testing may be completed by a local laboratory at the investigator's discretion.

Please refer to Section 7.1 for detailed contraception requirements.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study and for 30 days after the last dose of study drug. This may be signed by the legally authorized representative of the subject.

All sexually active female subjects of childbearing potential must have a negative urine or serum human chorionic gonadotropin (hCG) pregnancy test at Screening (Visit 1) before receiving any dose of study drug. Additional pregnancy tests (urine only) may be performed by local

laboratory throughout the study at the investigator's discretion. During the study, subjects will receive continued guidance with respect to the avoidance of pregnancy and ova or sperm donation as part of the study procedures. An additional serum hCG pregnancy test will be performed at the subject's last clinic visit.

9.1.13 ECG Procedure

ECGs may be obtained locally by HCP or PCP.

A 12-lead ECG will be recorded as indicated in Appendix A. If subjects receive the soticlestat dose in the clinic, the ECG should be performed approximately 30 min (±10 min) after dosing. If the subject cannot tolerate being supine, a sitting ECG may be obtained. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The interpretation of the ECG will be recorded in the source documents and in the eCRF. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval with QTcF (corrected QT interval). ECG traces recorded on thermal paper will be photocopied to avoid degradation of trace over time.

9.1.14 Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior assessments may be conducted via video, phone, or telehealth/telemedicine by a qualified rater from the clinical site.

Suicidal ideation and behavior will be assessed in subjects at least 6 years of age using 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) [5].

Two versions of the C-SSRS will be used in this study, the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS. C-SSRS scale will be provided to clinical sites electronically or paper copy via courier. C-SSRS may not be provided to the subject and/or subject's caregiver.

Study staff trained in the administration of the C-SSRS will assess subject suicidality using the C-SSRS, eliciting answers from the subject or the subject's legal representative. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator.

If a subject exhibits signs of suicidal ideation, the subject may be discontinued as described in Section 7.4.1.

9.1.15 Aberrant Behavior Checklist

The Aberrant Behavior Checklist assessment may be conducted via video, phone, or telehealth/telemedicine by a qualified rater from the clinical site.

Behavior will be assessed with the ABC-C questionnaire, which is a rating scale that measures the severity of a range of problem behaviors commonly observed in individuals with intellectual

and developmental disabilities [6]. It is completed by the caregiver. It is an empirically developed scale designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals across 5 domains with 58 items: irritability, agitation, and crying (15 items); lethargy, social withdrawal (16 items); stereotypy (7 items); hyperactivity/noncompliance (16 items); and inappropriate speech (4 items).

ABC-C scale will be provided to clinical sites by site electronically or paper copy via courier and may also be provided electronically or via courier to the subject and/or subject's caregiver for reference during remote conduct of the scale via video, phone, or telehealth/telemedicine.

If the subject is unable to comply with the ABC-C due to the language barrier (eg, unavailability of validated test in subject's language) the investigator may also use clinical judgment to assess for behavior.

9.1.16 Vineland Adaptive Behavior Scale

The Vineland Adaptive Behavior Scale assessment may be conducted via video, phone, or telehealth/telemedicine by a qualified rater from the clinical site.

The VABS, 3rd edition, Parent Caregiver Form (VABS-3 Parent Caregiver Form), is a parent-report questionnaire of adaptive functioning or how an individual behaves in their day-to-day life at home and in the community [7]. It assesses adaptive functioning across 4 domains: motor, communication, daily living, and socialization. The interview takes about 20 minutes to complete.

VABS assessment will be provided to clinical sites electronically or paper copy via courier and may also be provided electronically or via courier to the subject and/or subject's caregiver for reference during remote conduct of the scale via video, phone, or telehealth/telemedicine.

If the subject is unable to comply with the VABS due to the language barrier (eg, unavailability of validated test in subject's language), the investigator may also use clinical judgment to assess for adaptive function and behavior.

9.1.17 Quality of Life in Childhood Epilepsy

The Quality of Life in Childhood Epilepsy assessment may be conducted via telehealth/telemedicine by a qualified rater from the clinical site.

The Quality of Life in Childhood Epilepsy is a parent-reported questionnaire that evaluates health-related quality of life in children ages 4 to 18 years old [8]. It contains 76 items with 16 subscales covering 7 domains of life function: physical activities, social activities, cognition, emotional wellbeing, behavior, general health, and general quality of life.

This scale will only be used for pediatric subjects.

Quality of Life in Childhood Epilepsy scale will be provided to clinical sites electronically or paper copy via courier and may be provided electronically or via courier to subject and/or subject's caregiver for reference during remote conduct of the scale via video, phone, or telehealth/telemedicine.

9.1.18 Sleep Disruption Numerical Rating Scale

The Sleep Disruption Numerical Rating Scale assessment may be conducted via video, phone, or telehealth/telemedicine by a qualified rater from the clinical site.

Sleep Disruption Numerical Rating Scale will be provided to clinical sites electronically or paper copy via courier and may be provided electronically or via courier to subject and/or subject's caregiver for reference during remote conduct of the scale via video, phone, or telehealth/telemedicine.

The subject's caregiver will be asked:

> "On a scale of '0 to 10', please circle the number that best describes your child's sleep disruption in the last week."

The markers range from 0 (slept extremely well) to 10 (unable to sleep at all). If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within 3 days.

9.1.19 Clinician's Clinical Global Impression of Severity

The Clinician's Clinical Global Impression of Severity assessment is not recommended to be conducted remotely but may be conducted if necessary via video, phone, telehealth/telemedicine (video conduct preferred, but not required) by a qualified rater from the clinical site.

Clinician's Global Impression of Severity scale will be provided to clinical sites electronically or paper copy via courier. The scale may not be provided to the subject and/or subject's caregiver.

The CGI-S is used to obtain an assessment of symptom severity. The CGI-S focuses on clinicians' observations of the subject's current cognitive, functional, and behavioral performance. The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (among the most severely ill subjects).

9.1.20 [redacted]

[redacted]

9.2 Documentation of Screen Failure

Investigators must account for all subjects with a signed informed consent. If the subject is found to be ineligible for the study at the Screening/Baseline Visit, the IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is to be recorded in the IWRS.

Subjects may be rescreened up to 2 times after consultation with the medical monitor.

Subject ID numbers assigned to subjects who fail screening should not be reused. If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject ID number and treated as a stand-alone subject.

9.3 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment into the study.

9.4 Laboratory Sample Collection

Collection and handling of laboratory samples will be described in a laboratory manual.

9.5 [redacted]

[redacted]

9.6 [redacted]

[redacted]

10.0 SAFETY EVALUATIONS

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the sponsor or designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.1 AEs

An AE is any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to this medicinal product.

The definition of an AE also covers medication errors and uses outside what is foreseen in the protocol only if an AE results from the error, including intentional misuse, abuse, and overdose of the product. Adverse events (including SAEs) associated with overdose should be reported

according to the procedure outlined in Section 10.2. In the event of drug overdose, the patient should be treated symptomatically.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

Takeda has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study drug are to be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

Seizures in this subject population will be measured using the seizure diary and seizure frequency as a primary study endpoint. For the purpose of this study, reporting of seizures should meet the AE/SAE reporting requirements. As seizures are considered a baseline condition, seizures should be reported as an AE/SAE if: (1) there is a clear increase in the frequency of seizures compared to the subject's baseline, (2) there is an emergence of a new seizure type, or 3) the subject experiences status epilepticus, and any other time the investigator feels the seizure should be captured as an AE/SAE, in which case the investigator should document his/her reasoning. All seizures will be captured in the seizure diary collected at the site during the study and will be analyzed by the sponsor along with the reportable SAEs in evaluating risk:benefit. The sponsor will report the SAE events of seizure that meet these criteria in an aggregated unblinded report at the conclusion of the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. If a subject experiences an AE after signing informed consent, but prior to receiving study drug, the event will be reported, but will be included in the subject's medical history unless the event is serious, or the investigator feels the event may have been caused by a protocol procedure.

In addition, all AEs occurring after the subject receives the first dose of study drug must be reported to Takeda or its designee via the eCRF.

For subjects with ongoing AEs in the antecedent study, their ongoing AE should be recorded as medical history in this OLE study.

10.1.1 Severity Assessment

Investigators will be instructed to rate the severity of AEs using the following criteria:

Mild	Events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate	Events result in a low level of inconvenience or concerns with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe	Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Change in severity of an AE should be documented based on specific guidelines in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE.

10.1.2 Causality Assessment

Investigators will be instructed to report to the sponsor or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study drug via the eCRF.

An investigator causality assessment must be provided for all AEs (both serious and nonserious). This assessment must be recorded in the eCRF and any additional forms as appropriate.

Relationship of AEs to the defined study treatment (soticlestat [after the start of soticlestat on Day 1]), will be determined by the investigator according to the following criteria. Please note that not all criteria must be present to be indicative of a particular relationship.

Not Related	Exposure to the defined study treatment did not occur, or the occurrence of the AE is not reasonably related in time
Unlikely Related	The AE occurred in a reasonable time after the defined study treatment and is doubtfully related to the investigational agent/procedure
Possibly Related	The defined study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the defined study treatment
Related	The defined study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the defined study treatment than by other causes, or the defined study treatment was the most likely cause of the AE

If a subject's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to the sponsor or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.1.3 SAEs

SAE collection begins after the subject has signed informed consent. If a subject experiences an SAE after signing informed consent, but prior to receiving study drug, the event will be reported, but will be classified as a pretreatment SAE unless the investigator feels the event may have been caused by a protocol procedure.

Planned surgeries and/or hospitalizations should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert the sponsor or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

An SAE is any AE from this study that results in 1 or more of the following outcomes:

- Results in death.
- Requires or prolongs hospitalization.
- Is life-threatening (that is, immediate risk of dying).
- Persistent or significant disability/incapacity.
- Congenital anomaly or birth defect.
- Other medically important serious event.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs occurring up to and including the subject's last study visit will be collected, regardless of the investigator's opinion of causation.

10.1.4 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study drug or procedure. United States 21 Code of Federal Regulations 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. The sponsor has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

10.2 Reporting AEs

All nonserious AEs must be recorded in the eCRF upon awareness.

Any AE that meets SAE criteria (Section 10.1.3) must immediately (ie, within 1 business day) be sent to the sponsor upon learning of any SAE that occurs (whether or not attributable to the study drug). It is the investigator's responsibility to ensure that SAE reporting procedures are followed appropriately. All SAE reports and any revisions to an SAE report must be sent by fax or email.

All supporting source information concerning the SAE (eg, hospital records) should also be provided by fax or email.

Country-specific fax numbers and email addresses will be provided in a separate document.

If there is a question concerning an SAE, the site needs guidance regarding the reporting of an SAE, the site is returning a call from a sponsor safety specialist, or the site urgently needs to report an SAE or make the sponsor aware of an SAE, the safety hotline should be used (country-specific hotline numbers provided in a separate document).

If an SAE is reported via the hotline, the site should first submit the SAE paper form and then enter the SAE in the eCRF. Any AE that meets SAE criteria must be entered into the electronic data capture (EDC) system immediately (ie, within 1 business day) after site personnel first learns about the event in addition to faxing/emailing the SAE report form. Once the qualifying SAE data are entered into EDC, the sponsor will be notified by an email alert, which will contain high-level safety information. If a site makes an initial report of an SAE by the safety hotline, the site must subsequently enter all applicable information into the EDC system immediately thereafter.

All SAEs must be reported starting from the time that informed consent for study participation is provided. If the investigator becomes aware of an SAE within 30 days after the patient's last dose of study drug or within 30 days after the last study visit, the SAE must be reported. SAEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (ie, the patient or health care practitioner is unable to provide additional information, or the patient is lost to follow-up). SAEs that occur more than 30 days after the last dose of study drug or more than 30 days after the last study visit, do not need to be reported unless the investigator considers them related to study drug.

10.2.1 Sponsor Reporting Requirements

The sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use Section 6 of the current IB as the Reference Safety Information. The expectedness and reporting criteria of an SAE will be determined by the sponsor from the Reference Safety Information.

10.2.2 Investigator Reporting Requirements

The investigator must fulfill all local regulatory obligations required for the study investigators. It is the principal investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all SUSAR events that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs.

For blinded studies, investigators will receive blinded information unless unblinded information is judged necessary for safety reasons.

10.3 Exposure During Pregnancy and/or Lactation

Soticlestat should not be administered to pregnant or lactating females because the potential for adverse reactions to soticlestat in pregnant females, fetuses, and nursing infants is unknown.

If any subject is found to be pregnant during the study, she should be withdrawn and the study drug should be immediately discontinued.

Pregnancy data will be collected during this study for all subjects. Exposure during pregnancy (also referred to as exposure in-utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

Exposure during pregnancy must be recorded and the subject followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the subject discontinues study drug or discontinues from the study.

If a subject within this study or a subject's partner becomes pregnant while treated or exposed to study drug, the investigator must submit a pregnancy form to the sponsor via the same method as SAE reporting. Pharmacovigilance will supply the investigator with a copy of a "Pregnancy Reporting and Outcome/Breast Feeding" Form. When the outcome of the pregnancy becomes known, the form should be completed and returned via the same methods as for SAE reporting. If additional follow-up is required, the investigator will be requested to provide the information.

Exposure of an infant to a sponsor product during breastfeeding must also be reported and any AEs experienced by the infant must be reported to the sponsor Pharmacovigilance or designee via the same methods as for SAE reporting (Section 10.1.3).

Pregnancy is not regarded as an AE unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet criteria for an SAE (such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.4 Safety Monitoring

The sponsor's medical monitor and/or Pharmacovigilance physician will monitor safety data throughout the course of the study.

An independent Data Monitoring Committee (iDMC) will monitor the subjects' safety (see Section 11.0).

10.4.1 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 times the ULN on 2 consecutive occasions, the abnormality should be recorded as an AE.

If a subject is noted to have ALT or AST >3 times the ULN and total bilirubin >2 times the ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2. The investigator must contact the medical monitor for discussion of the relevant patient details and possible alternative etiologies, such as acute viral

hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests must also be performed. In addition, clinically significant liver function test increases are to be recorded in the AE page and if considered an SAE must follow the SAE process.

10.7 Appropriateness of Measurements

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with DEE.

11.0 STUDY-SPECIFIC COMMITTEES

Details of the iDMC will be captured in the iDMC charter before the start of the study. An iDMC will monitor the subjects' safety in accordance with the iDMC charter, details of which will be captured before the start of the study. The iDMC will consist of at least 3 external, independent, nonsponsor experts responsible for monitoring the safety data to ensure that the study does not pose unacceptable risks to the subjects.

12.0 DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by email, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

In addition, the sponsor or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs/IECs with direct access to original source documents.

12.1 Data Collection and Storage

All clinical raw data will be recorded promptly, accurately, and legibly, either directly into the data capture system as e-source data, or indelibly on paper (eg, ECG readings). A detailed list of the type (electronic or paper) and location for all source data will be included in the Trial Master File. When recorded electronically, case report forms will be electronically generated. All raw data will be preserved to maintain data integrity. The investigator or designee will assume the responsibility of ensuring the completeness, accuracy, and timeliness of the clinical data.

The EDC system is fully validated and Code of Federal Regulations Title 21 Part 11 compliant. The EDC system will maintain a complete audit trail of all data changes. At each scheduled monitoring visit, the investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each subject receiving study drug or placebo.

The investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/IEC to have direct access to all documents pertaining to the study.

13.0 STATISTICAL METHODS AND PLANNED ANALYSES

13.1 General Considerations

All statistical analyses will be performed using SAS® software (SAS Institute Inc, Cary, NC) Version 9.4 or higher. All clinical study data will be presented in subject data listings. Data summaries will be presented for all endpoints and will include descriptive statistics (number of subjects [n], mean, SD, first quartile [Q1], median, third quartile [Q3], minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number of missing will be presented, but without a percentage.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan which will be finalized and approved prior to database lock. Additional exploratory analyses of the data may be conducted as deemed appropriate.

13.2 Determination of Sample Size

No formal sample size calculation has been performed for this extension study. A study size of approximately 160 subjects is based on the estimated number of subjects ~~who are~~ expected to enroll from the antecedent soticlestat studies.

13.3 Definition of Baseline

Baseline for analyses is the baseline of the antecedent study, except for subjects who completed the antecedent study >15 days before the Screening Visit of this study, in which case the 4-week Baseline Period of this study will be used.

Unless otherwise specified in this section, all the summary tables by visit will use the values from the scheduled visit. The unscheduled visit may be used for the calculation of the overall change from baseline, for example, the worst change postdose.

13.4 Analysis Sets

13.4.1 Safety Analysis Set

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

In addition, subject disposition, demographics, and baseline characteristics will be summarized using the safety analysis set.

13.4.2 Intent-to-Treat Analysis Set

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

13.4.3 Modified Intent-to-Treat Analysis Set

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

13.5 Demographics and Baseline Characteristics

Demographic characteristics include age, gender, race, ethnicity, and study center. Baseline characteristics include baseline body weight and height). Summary statistics by treatment group and overall will include counts and percentages for discrete variables, and means, SD, Q1, medians, Q3, minimum, and maximum for continuous variables.

13.6 Subject Disposition

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

Disposition data will be summarized and provided in subject listings.

13.7 Concomitant Medications and Non-Pharmacologic Therapies and Procedures

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

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

13.8 Treatment Compliance

Treatment compliance will be summarized by daily dose over the entire treatment period. Compliance rates during the treatment period will be derived using the following formula:

100*(Total number of tablets/mini-tablets dispensed – Total number of tablets/mini-tablets returned) / (Expected number of tablets/mini-tablets)

Compliance rates will be presented for the safety analysis set using summary statistics and percentage for the frequency distributions (0% to <20%, 20% to 40%, 40% to <60%, 60% to <80%, 80% to <100%, 100% to ≤120%) by daily dose and overall.

13.9 Safety Analyses

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

The number and percentage of subjects with C-SSRS assessments of suicidal ideation and behavior will also be summarized.

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

The following definitions will be used for AEs:

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

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

Prior and concomitant medication use will be summarized by World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification system. Listings will be provided for all concomitant medications.

All data will be listed by subject.

13.10 Efficacy Analyses

Descriptive statistics will be used to summarize all efficacy endpoints (seizure frequencies over a 28-day period and CGI-S). Two-sided 95% CIs will be presented where meaningful. Seizure frequencies will be derived from data in seizure diaries collected throughout the study. Changes in drop, convulsive, and motor seizure frequency will be calculated and summarized.

Convulsive seizures include generalized tonic-clonic, focal to bilateral tonic-clonic with impaired awareness, and simultaneous bilateral clonic (generalized clonic) seizures. In subjects with DS, hemi-clonic seizures will be counted as convulsive seizures.

Drop seizures are defined as involving the entire body, trunk, or head that leads to a fall, injury, slumping in a chair, or head hitting a surface, or that could have led to a fall or injury, depending on the position of the subject at the time of the seizure or spell. Examples of seizures causing drop include, but are not limited to, atonic, clonic, and tonic seizures.

Motor seizures include drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, and focal seizures with bilateral hyperkinetic motor features. Isolated myoclonic seizures are excluded.

13.11 Exploratory Analyses

Descriptive statistics will be used to summarize exploratory endpoints (quality-of-life assessments – Quality of Life in Childhood Epilepsy score, Sleep Disruption Numerical Rating Scale, [redacted]). Two-sided 95% CIs will be presented where meaningful.

[redacted]

13.12 Other Statistical Issues

13.12.1 Significance Levels

Not Applicable. There will be no formal hypothesis testing for this study.

13.12.2 Missing or Invalid Data

Techniques for handling missing information with respect to reporting of seizures in the treatment period (Dose Optimization and Maintenance) will be specified in detail in the statistical analysis plan.

13.13 Ad hoc/Interim Analyses

Ad hoc and/or interim analyses may be performed at the discretion of the sponsor to facilitate planning of the soticlestat development program. Final analyses will be performed after the last subject completes the study and the database is locked.

14.0 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

14.1 Informed Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

14.2 Ethical Review

The sponsor or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on GCP.

Documentation of IRB/IEC approval of the protocol and the ICF must be provided to the sponsor before the study may begin at the investigative site(s). The IRB/IEC(s) will review the protocol as required.

The study site's IRB/IEC(s) should also be provided with the following:

- The current IB and updates during the study.
- ICF.
- Relevant curricula vitae.

14.3 Regulatory Considerations

This study will be conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- The ICH GCP Guideline (E6).
- Applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable IRB/IEC(s).

Some of the obligations of the sponsor may be assigned to a third-party organization.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other study-related data.

14.4 Confidentiality

The sponsor affirms that subject's rights to protection against invasion of privacy are in compliance with ICH and other local regulations (whichever is most stringent). Information about subjects and their records will be kept confidential by the sponsor and its representatives. Study-related records identifying subjects will be kept confidential and, to the extent permitted by applicable laws and/or regulations will not be made publicly available.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject and/or subject's custodial parent or guardian, except as necessary for monitoring and auditing by the sponsor, its designee, Food and Drug Administration (FDA), Health Authorities, Ethics Committees, and/or IRBs.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

If any of the results of the study are published, subject's identity will remain confidential.

The sponsor requires the investigator to permit sponsor representatives and, when necessary, representatives from FDA and other regulatory authorities, monitor, auditor, IRB to have access to study-related medical records in accordance with local privacy laws.

14.5 Investigator Information

Physicians with a specialty in neurology and/or epilepsy disorders will participate as investigators in this clinical study.

14.6 Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a sponsor representative.

14.7 Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer (or designee) and statistician will approve the final clinical study report for this study, confirming that, to the best of their knowledge, the report accurately describes the conduct and results of the study.

14.8 Publication Policy

The full terms regarding publication of the results of this study are outlined in the Clinical Study Agreement, Statement of Agreement, or the Master Clinical Study Agreement. Publication is permitted only after multi-center results are available and all disclosure requirements for clinical study registries have been met. Any data to be submitted for publication, including abstract submissions or presentations, are required to be submitted to Takeda for review at least 30 days prior to submission.

15.0 LIST OF REFERENCES

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[redacted]

Appendix A Schedule of Study Procedures

Assessment	Screening/ Baseline[a]	Year 1						Year 2				Year 3				Year 4+	Follow-up
Study Week(s)	**-4 to -1**	**1**	**4**	**12**	**24**	**36**	**48**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**	**Every 26 weeks**	**EOM+4**
Study Day(s)	**-28 to -1**	**1**	**29**	**85**	**169**	**253**	**337**	**456**	**547**	**638**	**729**	**820**	**911**	**1002**	**1093**	**--**	**EOM+28**
Visit Windows (Days)		**±3**	**±7**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±7**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**--, EOM**	**--**
Informed Consent/Assent	X																
Inclusion/Exclusion	X																
Medical history[b]	X																
Concomitant medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological examination[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum/urine pregnancy test[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood samples for hematology and serum chemistry	X	X			X		X		X		X		X		X	X	
[redacted]																	

Assessment	Screening/ Baseline[a]	Year 1						Year 2				Year 3				Year 4+	Follow-up
Study Week(s)	**-4 to -1**	**1**	**4**	**12**	**24**	**36**	**48**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**	**Every 26 weeks**	**EOM+4**
Study Day(s)	**-28 to -1**	**1**	**29**	**85**	**169**	**253**	**337**	**456**	**547**	**638**	**729**	**820**	**911**	**1002**	**1093**	**--**	**EOM+28**
Visit Windows (Days)		**±3**	**±7**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±7**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**--, EOM**	**--**
Serum sample for AED analysis		X			X		X		X		X		X		X	X	
12-lead ECG[g]	X				X		X		X		X		X		X	X	
Dispense seizure diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X[h]	
Collect seizure diary data	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X[h]	X
Contact IWRS for subject ID/medication ID/subject status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X[h]	
Study drug return for compliance/ accountability			X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X[h]	X
CGI-S	X	X			X		X		X		X		X		X	X	X
C-SSRS	X	X			X		X		X		X		X		X	X	
VABS	X				X		X		X		X		X		X	X	
ABC-C	X				X		X		X		X		X		X	X	
QoLCE	X	X			X		X		X		X		X		X	X	
SDNRS	X	X			X		X		X		X		X		X	X	

Assessment	Screening/ Baseline[a]	Year 1						Year 2				Year 3				Year 4+	Follow-up
Study Week(s)	**-4 to -1**	**1**	**4**	**12**	**24**	**36**	**48**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**	**Every 26 weeks**	**EOM+4**
Study Day(s)	**-28 to -1**	**1**	**29**	**85**	**169**	**253**	**337**	**456**	**547**	**638**	**729**	**820**	**911**	**1002**	**1093**	**--**	**EOM+28**
Visit Windows (Days)		**±3**	**±7**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±30**	**±7**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**--, EOM**	**--**
[redacted]																	

[redacted]; ABC-C, Aberrant Behavior Checklist-Community Edition; AED, antiepileptic drug; CGI-S, Clinician's Clinical Global Impression of Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; eCRF, electronic case report form; EOM, end of Maintenance Period; ID, identification number; IWRS, interactive web response system; [redacted]; QoLCE, Quality of Life in Childhood Epilepsy; SDNRS, Sleep Disruption Numerical Rating Scale; VABS, Vineland Adaptive Behavior Scale.

After 4 years of participation in the study (at the Week 208 visit), subjects will be re-evaluated: the first visit in Year 4 will be scheduled for Week 182. Subjects may continue the use of soticlestat as the discretion of the investigator, until development is stopped by the sponsor, or the product is approved for marketing, or at any time at the discretion of the sponsor. Starting with the subject's last visit on the maintenance dose, the subject will begin an up to 2-week period of dose tapering that will be followed approximately 2 weeks later by the Follow-up Visit. A subject who decides to terminate treatment between scheduled visits should be scheduled for an EOM visit, have visit assessments performed, be started on dose tapering, and have a follow-up visit scheduled.

[a] The Screening/Baseline visit may occur within 15 days of the end of treatment visit for the antecedent study and may occur on the same day. Identical assessments taken at the subject's last visit of the antecedent study do not need to be repeated at Visit 1 of this study if these 2 visits are ≤30 days apart. Baseline evaluations are to be done for subjects who completed the antecedent study >30 days before Screening in this study. The last visit in the antecedent study can be combined with the screening/baseline visit and Visit 2 (Day 1) in this study.

[b] Medical history data from antecedent studies may be carried over and recorded in the eCRF in this study if these data are available; otherwise, new medical history data should be collected at the Screening Visit of this study. For subjects with ongoing adverse events in the antecedent study, their ongoing adverse events should be recorded as medical history in this open-label extension study.

[c] Concomitant medication data from antecedent studies may be carried over and recorded in the eCRF in this study if these data are available; otherwise, new concomitant medication data should be collected at the Screening Visit of this study.

[d] Eye examination (including fundoscopy, best corrected visual acuity, and visual field assessments) as part of the neurological examination.

[e] Additional pregnancy tests (urine only) may be performed throughout the study at the investigator's discretion. A serum (rather than urine) pregnancy test will be performed at the subject's last clinic visit.

[redacted]

[g] ECGs will be conducted and analyzed locally according to the site's standard operating procedures. If subjects receive the soticlestat dose in the clinic, the ECG should be performed approximately 30 min (±10 min) after dosing.

[h] After Visit 15 and after every visit thereafter within the Maintenance Period, 4-month supplies of study drug and seizure diaries may be delivered to participants 3 months before the next scheduled visit. Promptly after receiving these supplies, participants will return unused study drug and completed seizure diaries to their study sites.

[redacted]

Appendix B Strong CYP3A Inducers and Inhibitors

Strong inducers and inhibitors of CYP3A are prohibited, except antiseizure medications. Examples are listed below.

Strong Inducers of CYP3A	Strong Inhibitors of CYP3A
Apalutamide	Boceprevir
Enzalutamide	Cobicistat
Mitotane	Danoprevir and ritonavir
Rifampin	Elvitegravir and ritonavir
St. John's wort	Grapefruit juice
	Indinavir and ritonavir
	Itraconazole
	Ketoconazole
	Lopinavir and ritonavir
	Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
	Posaconazole
	Ritonavir
	Saquinavir and ritonavir
	Telaprevir
	Tipranavir and ritonavir
	Telithromycin
	Troleandomycin
	Voriconazole
	Clarithromycin
	Idelalisib
	Nefazodone
	Nelfinavir

Source: fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Inhibitors, Table 3-3; inducers, Table 3-2. Accessed 06 June 2021.

Appendix C Study Management During COVID-19 Pandemic

The purpose of this section is to safeguard the safety of study subjects, ensure continuation of study conduct and uninterrupted maintenance of treatment, and preserve the integrity of the study, in case of a general public health crisis or pandemic, such as COVID-19. This section addresses situations in which scheduled in-person clinic visits are not feasible due to local, regional or national restrictions.

The principal investigator holds the ultimate responsibility for the safety and well-being of study subjects and shall maintain compliance with the current local and health authority guidelines and recommendations pertaining to the pandemic. The study procedures outlined in this protocol may be modified subsequently according to any emerging or revised health authority guidelines during conduct of the study due to the ongoing COVID-19 pandemic. These modified study procedures are to be used only during the COVID-19 pandemic.

Due to the COVID-19 pandemic, study subjects may not be able to attend scheduled in-person clinic visits as per protocol. All investigational sites should follow local and country health and government authorities' restrictions and recommendations on conduct of clinical studies during the pandemic.

The study design includes virtual visits except for baseline, and randomization/dosing visits, in the event an in-person visit is not possible for the planned clinic visits and in alignment with institutional or local guidelines, comfort level of site staff, and caregiver/family willingness to travel, virtual visits are allowed for these 2 visits to monitor subject safety. During the COVID-19 pandemic, sites are encouraged to discuss subjects and their continued virtual participation with the medical monitor. COVID-19 vaccination of subjects is allowed during the study.

Video, phone, or telehealth/telemedicine options will be used to conduct the virtual visits. The site will ensure that any related subject data privacy aspects are appropriately managed and will obtain subjects' consent for the use of virtual visits.

ECGs, clinical laboratory samples, and physical examinations may be performed/collected and analyzed by a local laboratory/facility at the investigator's discretion with results sent to the clinical site.

In case subjects are not able to attend the planned clinic visits, Direct to Patient study drug shipment may be considered using a specialized courier vendor. A process has been put in place to ensure shipment traceability, proper temperature control conditions, intellectual property return and accountability should be properly managed to ensure that any related subject data privacy aspects are appropriately covered. The investigator will obtain subject's consent to Direct to Patient study drug shipment and the use of their personal data to that effect.

Any protocol deviations, missing visits, or missing assessments related to COVID-19 restrictions will be recorded and reported in the clinical study report.

In case of prolonged access restrictions to external visits (study monitors) to an investigative site due to COVID-19 pandemic and wherever possible by local regulations, remote source data

verification may be considered for critical data related to subject's safety and any key variables to ensure data accuracy/integrity.

If remote source data verification is required, full details of the process will be included the clinical monitoring plan following any applicable local guidance for secure access to remote source documents and data security provisions to protect personal data.

Appendix D Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each (e)consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an (e)consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and destruction locally at site (if approved by sponsor or designee) or return of all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix E Protocol History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
24 August 2021	Amendment 4	Substantial	Global
14 August 2020	Amendment 3	Substantial	Global
13 February 2020	Amendment 2	Substantial	Global
28 May 2019	Amendment 1 ES v1	Substantial	Spain
11 February 2019	Amendment 1	Substantial	Global
16 April 2018	Initial version	Not applicable	Global

Rationale for Amendment 3

This document describes the changes in reference to the protocol incorporating amendment No. 3. The primary reasons for this amendment are to define the acceptable changes to study procedures related to the COVID-19 pandemic.

Changes Implemented by Amendment 3

The following major changes were implemented for this amendment:

- Revised objectives (Synopsis [Section 2] and Section 6) to state objectives are to assess soticlestat when administered as adjunctive therapy to at least one anti-seizure therapy.
- Updated treatment section (Section 9.2.3) to include recalibration of weight-based dosing every 6 months for pediatric subjects during the maintenance period, to ensure that the dose is weight-appropriate.
- Added a new section (Section 10.1 and Appendix 5) for the modified procedures instituted in response to the COVID-19 pandemic.
- Clarified that the visit number, dose level, time of last dose and time of blood sampling following the last dose will be recorded in the eCRF. The time of the last meal will also be recorded in the eCRF (Section 10.5.1).
- Updated statistical section (Section12.3) to clarify the baseline seizure definition, analysis sets (Section 12.4) and ad hoc/interim analyses (Section 12.13).
- [redacted]

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only. The synopsis was edited to reflect the changes implemented in the protocol. A detailed description of and rationale for changes implemented by Amendment 3 are provided in Appendix 5.

Rationale for Amendment 2

This document describes the changes in reference to the protocol incorporating amendment No. 2. The primary reasons for this amendment are to extend the Maintenance Period (including additional scheduled clinic visits 26 weeks apart) and amend the visit schedule after Year 1, amend the visit schedule of assessments, incorporate changes initiated by administrative letters, and resolve inconsistencies with antecedent protocols.

Changes Implemented by Amendment 2

The following major changes were implemented for this amendment:

- Amended the title of the protocol.
- Changed the frequency and timing of visits in Year 2 and extended the Maintenance Period past Year 2.
- Added new secondary objectives.
- Added new secondary endpoints.
- Clarified that inclusion criterion 2 is not applicable to Spain.
- Added the option of administering TAK-935 by jejunostomy tube.
- Amended contraception and pregnancy avoidance text.
- Revised the pregnancy avoidance period and text.
- Provided for recalibration of dose with current weight for pediatric patients.
- Added a criterion for patient discontinuation related to prolongation of a corrected QT interval.
- Added a criterion for patient discontinuation related to suicidal ideation.
- Revised the text for investigator decision for patient discontinuation.
- Defined a missed dose.
- Clarified that all identical assessments at the last visit of an antecedent protocol ≤30 days before the Screening Visit in this study do not need to be repeated.
- Deleted the dosing card from the protocol.
- Clarified the eye examination and vision testing.
- Added an as-needed urine pregnancy test.
- Added the Clinician's Clinical Global Impression of Severity (CGI-S) to the objectives, assessments, and endpoints.
- [redacted]
- Amended the maximum blood volume collected per visit.

- [redacted]
- Replaced the interim analysis section with ad hoc analysis section.
- [redacted]
- Added an independent Data Monitoring Committee.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only. The synopsis was edited to reflect the changes implemented in the protocol. A detailed description of and rationale for changes implemented by Amendment 2 are provided in Appendix A.

Protocol Amendment 1 ES v1 was a local amendment and is not applicable to the global protocol.

Rationale for Amendment 1

This document describes the changes in reference to the protocol incorporating amendment No. 1. The primary reasons for this amendment are to incorporate changes initiated by administrative letters and resolve inconsistencies with the antecedent protocols.

Changes Implemented by Amendment 1

The following major changes were implemented for this amendment:

- Added [redacted] as a prohibited concomitant medication.
- Removed urinalysis from safety assessments.
- Added 2 new forms of approved contraceptive methods and clarified the duration of contraceptive use.
- Added a 4-week Screening/Baseline Period for pediatric patients who complete the antecedent study >15 days before the Screening Visit.
- Clarified the duration for avoidance of pregnancy and donation of sperm and ova for male and female patients, respectively.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only. A detailed description of and rationale for changes implemented by Amendment 1 are provided in Appendix 5.

Amendment 4 to A Phase 2, Prospective, Interventional, Open-Label, Multisite, Extension Study To Assess the Long-Term Safety and Tolerability of Soticlestat (TAK-935) as Adjunctive Therapy in Subjects With Developmental Epileptic Encephalopathies Including Dravet Syndrome, Lennox Gastaut Syndrome, CDKL5 Deficiency Disorder, and Chromosome 15 Duplication Syndrome (ENDYMION 1)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	27-Aug-2021 16:57 UTC
[redacted]	Biostatistics Approval	27-Aug-2021 19:09 UTC