# Clinical Study Protocol

NCT Number: NCT05163314

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

Study Number: TAK-935-3003

Document Version and Date: Amendment 2.0, 28 Feb 2023

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

**TAKEDA PHARMACEUTICALS**

**PROTOCOL**

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

**Amendment 2**

**Open-Label Extension Study of Soticlestat in Dravet and Lennox-Gastaut Syndromes**

| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda Development Center Americas, Inc.<br>95 Hayden Avenue<br>Lexington, MA 02421 USA | | |
| **Study Number:** | TAK-935-3003 | | |
| **IND Number:** | 133627 | **EudraCT Number:** | 2021-002482-17 |
| **Compound:** | Soticlestat (TAK-935) | **EU CT Number:** | 2022-502802-34-00 |
| **Date:** | 28 February 2023 | **Version/Amendment Number:** | Amendment 2 |

**Amendment History**:

| Date | Amendment Number | Amendment Type | Region |
|---|---|---|---|
| 28 February 2023 | Amendment 2 | Substantial | Global |
| 24 February 2023 | Amendment 1 DE v1 | Substantial | Germany |
| 02 November 2021 | Amendment 1 | Substantial | Global |
| 06 July 2021 | Initial version | Not applicable | Global |

# 1.0 ADMINISTRATIVE INFORMATION

## 1.1 Contacts

A separate contact information list will be provided in the study manual.

Takeda Development Center (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 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.

| | |
|---|---|
| PPD , MD | Date |
| PPD | |
| Neuroscience | |
| Takeda | |

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|---|---|
| PPD , PhD | Date |
| PPD | |
| Statistical and Quantitative Sciences | |
| Takeda | |

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert 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, 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 Conference on Harmonisation, E6 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 defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix D).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix F of this protocol.



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 2 Summary of Changes

### Protocol Amendment 1 DE v1 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 1 DE v1.

The primary reasons for Amendment 1 DE v1 were to:

- Reduce the blood volume collected during the study, including removal of antiseizure medication (ASM) level analysis.
- Describe measures implemented to reduce stress and pain and summarize low risk and burden of the study.
- Clarify that subjects (in Germany) must use highly effective contraception.

### Protocol Amendment 2 Summary and Rationale

The primary reasons for Amendment 2 are to:

- Add annual ophthalmological examinations after Year 1 to obtain long-term ophthalmological safety data per regulatory requirements.
- Allow doses between the original dose levels selected for this study after discussing with the sponsor to improve subject retention.
- Assess palatability and acceptability in children per regulatory requirements; incorporate clarifications necessary for compliance with the European Union (EU) Clinical Trials Regulation (CTR).
- Make contraception instructions consistent with antecedent protocols TAK-935-3001 and TAK-935-3002.



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.

| **Protocol Amendment 2, Incorporating Amendment 1 DE v1** | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Global Version of the Approved Protocol** | | | |
| **Change No.** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| **Changes made in Amendment 1 DE v1 (Germany), now apply to all countries unless otherwise indicated.** | | | |
| 1 | Section 4.3 Benefit/Risk Profile | Added information on unlikely risk of teratogenicity/fetotoxicity in early pregnancy. | Clarification added following Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) request to implement only highly effective contraception methods. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 2 | Section Inclusion Criteria7.1 (#5)<br>Section 9.1.17.3General Guidance With Respect to the Avoidance of Pregnancy<br>Appendix E Elements of the Subject Informed Consent | Removed "effective" methods of contraception, clarified that methods listed are "highly effective"; clarified that highly effective combined and progestogen-only hormonal contraceptives are those associated with inhibition of ovulation. | On request from BfArM to implement only highly effective contraception methods. |
| 3 | Section Procedures for Clinical Laboratory Samples9.1.7.3<br>Appendix G Blood Volumes | Blood volume collected at screening, unscheduled retests, and the total for scheduled visits was reduced.<br>Sites will be advised not to attempt collection of blood if they fail twice. Another attempt can be made after 2-4 weeks.<br>New appendix. | On request from BfArM, based on the recommendation of *Ethical considerations for clinical trials on medicinal products conducted with minors (18 Sep 2017).*<br>Appendix shows that the blood volume collect during each visit does not exceed 1% of the total blood volume, and the blood volume collected over any 4-week period does not exceed 3% of the total blood volume. |
| 4 | Section 9.4.1<br>Appendix A Schedule of Study Procedures | Remove antiseizure medication (ASM) level analysis. | Reduce volume of blood collected, per BfArM request. On the basis of the available and anticipated data from phase 2 and phase 3 studies, there are enough data to analyze the drug-drug interaction between soticlestat and other ASMs. Therefore, optional ASM level analysis is not needed in this study. |
| 5 | Appendix H Minimizing Stress and Pain for Study Subjects | Add new appendix describing measures implemented to reduce stress and pain; summarizes the overall low risk of soticlestat and the study procedures, and low burden to subjects and parents/caregivers. | On request from BfArM, based on the recommendation of *Ethical considerations for clinical trials on medicinal products conducted with minors (Revision 1 dated 18 Sep 2017).* |
| **Additional changes made in Amendment 2 (global)** | | | |
| 6 | Title page<br>Section 2.0 Study Summary | Add EU CT Number | European Union (EU) Clinical Trials Regulation (CTR) requirement. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 7 | Section 2.0 Study Summary<br>Section 6.1 Study Design<br>Section 13.2 Determination of Sample Size | Change number of estimated sites from 65 to 100.<br>Change number of estimated subjects from 376 to 400. | Reflects the increased number of subjects and sites in the ongoing TAK-935-3001 and TAK-935-3002 studies. |
| 8 | Section 4.2 Rationale for the Proposed Study | Add that no subjects or parents/caregivers were involved in the design of this study. | EU CTR requirement. |
| 9 | Section 2.0 Study Summary<br>Section 5.1.3 Exploratory Objectives<br>Section 5.2.3 Exploratory Endpoints<br>Section 6.1 Study Design<br>Section 6.2 Justification for Study Design, Dose, and Endpoints<br>Section 9.1.16 Assessing Palatability and Acceptability<br>Section 13.2.6 Exploratory/Additional Analyses<br>Appendix A Schedule of Study Procedures | Add assessment of palatability and acceptability in children. | Per regulatory requirements (European Medicines Agency, National Medical Products Administration), to assess and confirm palatability and acceptability of soticlestat administered as whole tablets or crushed and mixed with selected foods and liquids in subjects younger than 18 years. |
| 10 | Section 5.1.3 Exploratory Objectives<br>Section 5.2.3 Exploratory Endpoints<br>Section 13.2.6 Exploratory/Additional Analyses | Rephrase the objective and endpoint to "Days when rescue ASMs are used." | Proportion of days when rescue ASMs are used will be presented, instead of the number of days. In addition, the revision allows the flexibility of presenting this endpoint in clinically meaningful ways. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 11 | Section 5.1.3 Exploratory Objectives<br>Section 5.2.3 Exploratory Endpoints<br>Section 9.1.13.4 CCI [redacted]<br>Section 13.2.6 Exploratory/Additional Analyses<br>Appendix A Schedule of Study Procedures<br>Appendix I Substudy Synopsis/Procedures | CCI [redacted] | [redacted] |
| 12 | Section 13.2.6 Exploratory/Additional Analyses<br>Appendix I Substudy Synopsis/Procedures | Include a new appendix (Appendix I) to describe the details of the Optional Caregiver Qualitative Input Substudy. | To conduct an optional qualitative substudy with caregivers to explore the long-term outcomes of treatment with soticlestat.<br>The appendix clearly defines study objective, study design, data collection, analyses, etc. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 13 | Section 2.0 Study Summary<br>Section 5.2.1 Primary Endpoints—Safety | Delete "clinically significant" from one of the primary endpoint "Incidence of clinically significant/ abnormal safety laboratory test values, vital signs, and electrocardiogram (ECG) evaluations".<br>Delete the incidence of abnormal vital signs from the abovementioned primary endpoint.<br>Combine one of the primary endpoint on change from baseline in C-SSRS into another endpoint ("Change from baseline in clinical laboratory test values, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS), and ECG parameters").<br>Divide the last primary endpoint in Protocol Amendment 1 "Change from baseline in height and weight for all age groups, and in absolute value for Tanner stage for children 6 to 17 years and insulin-like growth factor 1 (IGF-1) for children 2 to 17 years of age during the study" into 2 separate endpoints. | Clinically significant abnormal safety laboratory test values, vital signs and ECG values will be reported as AEs, therefore already included in the first primary endpoint "Incidence of TEAEs". Therefore, changed one of the primary endpoints to "Incidence of abnormal … evaluations" to include both clinically significant and nonsignificant abnormalities.<br>The sponsor does not plan to analyze incidence of abnormal vital signs, as clinically significant ones will be included in "Incidence of TEAEs", and it does not add to scientific value to analyze the nonsignificant ones.<br>The sponsor plans to present subjects with shifts in clinical laboratory or ECG values, as these results are usually included as a part of safety outputs.<br>Rephrase the endpoint on C-SSRS and the endpoint on growth and maturation to be clearer and more reader-friendly. |
| 14 | Section 2.0 Study Summary<br>Section 6.1 Study Design | Clarify that dosing schedule is only based on weight. | Clarification. |
| 15 | Section 2.0 Study Summary<br>Section 6.1 Study Design<br>Section 6.1.2 Maintenance Period<br>Table 6.e Recommended Intermediate Doses Between Scheduled Dose Levels for Each Weight Band | Allow doses between the original dose levels selected for the study after discussing with the sponsor. | Provides dosing flexibility to improve subject retention, when subjects are not tolerating the higher dose level, but per investigators' judgement there has not been satisfactory efficacy observed with the lower dose level. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 16 | Section 2.0 Study Summary<br>Section 6.1 Study Design<br>Section 6.2 Justification for Study Design, Dose, and Endpoints<br>Section 7.1 Inclusion Criteria (#1) | Subjects from all antecedent soticlestat phase 3 clinical studies will roll over into this study (previously was only TAK-935-3001 and TAK-935-3002). | Extends rollover from any soticlestat phase 3 clinical study. |
| 17 | Section 2.0 Study Summary<br>Section 6.1 Study Design<br>Section 8.1.3 Dose and Regimen | Clarify that enteral feeding tubes are not limited to specific types. | Various enteral feeding tubes may be used in the target population. |
| 18 | Section 6.1.2 Maintenance Period | In extenuating circumstances that lead to unexpected study drug interruption for a relatively long time, the study drug dosing schedule after the situation improves and any unscheduled safety assessments will depend on the investigator's discretion, after the sponsor or the contract research organization medical monitor are consulted. | Allows flexibility to resume dosing after unexpected study drug interruption for a long time, which might happen in this long-term safety study. |
| 19 | Section 6.1.4 Overall Schedule of Study Assessments<br>Section 9.6.1 Unscheduled Visits<br>Appendix A Schedule of Study Procedures<br>Appendix C Virtual Visits and Trial Management During COVID-19 Pandemic and Other Extenuating Circumstances | Broaden option to have virtual visits to allow more flexibility for subjects or parents/caregivers who may have difficulties with travel for clinic visits, such as COVID-19 (coronavirus disease 2019) restrictions or other extenuating circumstances. Also allow virtual visits to be done as clinic visits. Allow home visits by site staff in jurisdictions that permit this. | Allows more flexibility for subjects or parents/caregivers. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 20 | Section 6.1.4 Overall Schedule of Study Assessments<br>Appendix A Schedule of Study Procedures | Add that subjects rolling over from prior open-label phase 3 studies can directly start from the maintenance period, and the treatment period in the antecedent study will be counted into the maintenance period of this study (for example, if the treatment period in the antecedent study is 1 year, the subjects will start from Year 2 after rolling over to this study). | Subjects from open-label antecedent studies have been exposed to soticlestat for a relatively long period, therefore, less frequent visits are needed. |
| 21 | Section 6.4 Poststudy Access<br>Section 9.6.2 Poststudy Care | Clarification added that the study design and duration allows the study to continue until soticlestat is approved and launched. | EU CTR requirement. |
| 22 | Section 7.1 Inclusion Criteria (#3) | Provide for inclusion of subjects living in residential facilities to participate. | Allows flexibility for subjects who live in residential facilities with professional caregivers to participate. The professional caregivers could perform relevant assessments including seizure and medication diaries and health outcome measures. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 23 | Section 7.1 Inclusion Criteria (#4)<br>Section 9.1.1 Informed Consent Procedure<br>Section 12.2 eCRFs<br>Section 12.3 Record Retention<br>Section 14.1 Study-Site Monitoring Visits<br>Section 15.1 IRB and/or IEC Approval<br>Section 15.2 Subject Information, Informed Consent, and Subject Authorization<br>Section 15.3 Subject Confidentiality<br>Appendix D Responsibilities of the Investigator | All electronic (e)consent changed to consent. | Corrects the mistaken mention of (e)consent in Protocol Amendment 1. |
| 24 | Section 7.1 Inclusion Criteria (#5)<br>Appendix E Elements of the Subject Informed Consent | Clarify allowed contraceptive methods. | Clarifies that highly effective contraceptive methods, as well as effective contraceptive methods (not applicable for Germany), are allowed. In Protocol Amendment 1 the term "effective" was used to cover both type of methods. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 25 | Section 7.3 Excluded Medications<br>Section 7.4 Diet, Fluid, and Activity Control<br>Appendix B Strong CYP3A Inducers | Remove inhibitors of cytochrome P450 (CYP)3A from the prohibited medications and from the appendix.<br>Delete prohibition of fruit and juice of grapefruit, Seville oranges, and starfruit.<br>Allow topical CYP3A inducers. | Per pharmacokinetic (PK) results from a recently completed DDI study (TAK-935-1007), the effect of a strong CYP3A4 inhibitor, itraconazole, on the PK exposure measures of soticlestat is small (<25% on maximum concentration and area under the plasma concentration-time curves). This suggests that there is no need to exclude strong CYP3A4 inhibitors, which will now be allowed in the study. This also includes the fruit and juice of grapefruit, Seville oranges, and starfruit.<br>While a strong CYP3A inducer is expected to significantly reduce soticlestat exposure, the DDI potential of a topical formulation with soticlestat is expected to be minimal. Therefore, topical CYP3A inducers are allowed. |
| 26 | Section 8.1 Study Drug and Materials | Identify soticlestat as the investigational medicinal product. State that there are no auxiliary medicinal products. Add table describing characteristics of the intervention (soticlestat). | EU CTR requirements. |
| 27 | Section 8.1.1.1 Study Drug | Add requirements for study drug labeling, including changes that would be disallowed and traceability information. | EU CTR requirements. |
| 28 | Section 8.3 Accountability and Destruction of Sponsor-Supplied Drugs | Add information for destroying unused drug at study site. | Clarification. |
| 29 | Section 9.1.2 Demographics, Medical History, and Medication History Procedure<br>Appendix A Schedule of Study Procedures | Clarify that TEAEs from the antecedent study that are still ongoing at the time of consent for this study will be captured as medical history. | Clarification. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 30 | Section 9.1.5 Physical Examination Procedure<br>Section 9.1.6 Neurological Examination Procedure | Clarify that subitems in the physical and neurological assessments should be completed as much as possible, and that if certain subitems cannot be completed due to the subject's inability to cooperate, the reason should be documented. | Allows flexibility because it may be challenging to complete certain assessments due to the intellectual, developmental, or physical disability of the subjects. |
| 31 | Section 9.1.7.1 Ophthalmological Evaluation Procedure<br>Section 9.3.4 Reporting of Cataracts<br>Appendix A Schedule of Study Procedures | Add preference to obtain a picture of the fundus from ophthalmoscopy.<br>Add ophthalmological examination to be conducted annually (at Day -1, Week 52, Week 104, and every 52 weeks afterwards, until the study ends).<br>Clarify that discontinued subjects should have ophthalmological evaluation at the early termination visit. | Provides visual record of ophthalmological examination results, to be consistent with the requirement of the antecedent studies.<br>Obtain long-term ophthalmological safety data per regulatory requirements (Pharmaceuticals and Medical Devices Agency, Agenzia italiana del farmaco).<br>Ophthalmological evaluation at the early termination visit was omitted in Protocol Amendment 1. |
| 32 | Section 9.1.7.3 Procedures for Clinical Laboratory Samples, Table 9.a | Add footnote that urinalysis is the primary method. Urine dipstick may be used as a backup only.<br>Add footnote that only subjects rolling over from the TAK-935-3001 and TAK-935-3002 antecedent studies, who are aged 2 to 17 years during the study, should be tested for insulin-like growth factor 1 (IGF-1) levels. | Urine samples in test tubes may be difficult to collect from subjects with cognitive dysfunction and seizures. Urine dipstick offers an alternative way to perform urinalysis.<br>IGF-1 level analysis is only relevant to pediatric subjects with Dravet syndrome or Lennox-Gastaut syndrome (LGS) from studies TAK-935-3001 and TAK-935-3002. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 33 | Section 9.1.7.3 Procedures for Clinical Laboratory Samples, Table 9.a | Clarify that if subjects experience alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, prothrombin time will be included in the follow-up laboratory tests. | Prothrombin time was offered but previously omitted in the list of follow-up laboratory test for subjects with increased hepatic enzymes. |
| 34 | Section 9.1.10 Clinical Assessment of Suicidal Ideation and Behavior | Clarify that children younger than 6 years at the start of the study will be evaluated with Columbia-Suicide Severity Rating Scale (C-SSRS) if and when they turn 6 years old during the study. | Allows C-SSRS assessment of this additional group of children. |
| 35 | Section 9.1.11 Seizure Frequency | All seizure events will be recorded starting on the day after Visit 1 (Day 1), rather than at Visit 1. | Clarifies that seizure recording will start from Day 1 as the first dose of study drug in this study starts from the morning of Day 1. |
| 36 | Section 9.1.12.3 CGI-I Seizure Intensity and Duration | Change "convulsive seizures" and "MMD seizures" to "the most impactful seizures." | Clinical Global Impression of Improvement Seizure Intensity and Duration measures the change of the most impactful seizures, which might not be convulsive seizures or major motor drop (MMD) seizures. |
| 37 | Section 9.1.13.1 Quality of Life Inventory-Disability (Parent/Caregiver Version) | Remove reference to translation and validation. | Translation and validation have been completed for all countries in the antecedent studies. |
| 38 | Section 9.1.1 Informed Consent Procedure<br>Section 9.1.14 Optional Blood Sample for Genetic Testing: Potential Exploratory Research<br>Appendix A Schedule of Study Procedures | Clarify that optional genetic samples for subjects with LGS will not be collected in France or Brazil, in addition to China. | Optional genetic samples are not allowed by the regulatory authorities in these countries. |
| 39 | Section 9.1.17.1 Male Subjects and Their Female Partners | Clarify that sperm donation by subjects is not allowed. | Per sponsor requirement, pregnancy of the subject's partner must be reported. This change is to overcome the difficulty of tracking and reporting pregnancy resulting from donated sperm. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 40 | Section 9.1.17.2 Female Subjects and Their Male Partners | Clarify definitions of nonfertile subjects. | Adds definition of nonfertile subjects per Takeda template. |
| 41 | Section 9.1.17.2 Female Subjects and Their Male Partners<br>Appendix A Schedule of Study Procedures | Clarify that for female subjects of childbearing potential, if the investigator judges it necessary, a local laboratory may be used to confirm a negative serum or urine pregnancy test result before the first dose of study drug. | Clarification. In the previous protocol versions there were no instructions on whether or not to confirm the pregnancy test results before the first dose. |
| 42 | Section 9.1.18 Pregnancy | Add requirement to report pregnancy of female partners of male subjects. | There is no evidence suggesting any risk in pregnancy of female partners of male subjects. To be conservative, the sponsor will follow up on such pregnancy and newborn information. |
| 43 | Section 9.3.5 Special Situation Reporting | Provide definitions and reporting instructions for abuse, misuse, and medication error. | EU CTR requirements. |
| 44 | Section 9.4 Biomarker Samples | New section with table of primary specimen collections. | Takeda template requirement. |
| 45 | Section 9.4.1 Plasma Samples for Soticlestat PK<br>Section 9.4.2 Plasma Samples for Pharmacodynamic Measurements<br>Appendix A Schedule of Study Procedures | Clarify that collection of PK and PD samples applies only to subjects from an antecedent study that collected PK and pharmacodynamic samples. | These samples are not needed if there are no corresponding baseline from the antecedent study. |
| 46 | Section 9.4.3 Blood Sample for DNA Analysis | Describe rationale for DNA sampling. | Provides rationale for DNA research. |
| 47 | Section 9.5 Biological Sample Retention and Destruction | Add provision for storage of leftover blood samples for further research. | Corrects the omission in Protocol Amendment 1 text (but it was included in the informed consent forms for Protocol Amendment 1), per EU CTR requirements. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 48 | Section 10.1 Definitions | Clarify definitions to distinguish adverse events as treatment-emergent adverse events (TEAEs) or pretreatment events (PTEs).<br>Clarify that PTEs (for the current study) that are attributed to the antecedent study will be collected under the antecedent study. | Makes terminology consistent.<br>Clarification. |
| 49 | Section 10.1.2 Additional Points to Consider for AEs | Clarify that concurrent medical conditions should not be recorded as AEs. But a worsening or complication of a concurrent medical condition should be recorded as one. | Clarification. |
| 50 | Section 10.2.1.1 AE Collection Period | Clarify that the TEAE collection period commences from the first dose of study drug on Day 1. | The first dose of study drug is taken on the morning of Day 1 (the day after Visit 1), therefore, TEAEs should be reported after that. |
| 51 | Section 10.2.1.2 AE Reporting | Add reporting instructions for pretreatment events. | Clarification.<br>EU CTR requirement. |
| 52 | Section 10.2.2 Collection and Reporting of SAEs | Indicate that contacts for serious adverse event reporting are provided in the study manual. | Correction. |
| 53 | Section 12.1 Source Documents | New section; include brain imaging and electroencephalogram in list of source data to be reviewed and maintained. | Provides a designated section for this topic and adds additional document examples that are pertinent to this study. |
| 54 | Section 12.2 eCRFs | Note that no data will be entered directly into the electronic case report forms (eCRFs) as source data and identifies data that will not be recorded in the eCRFs. | EU CTR requirements. The site is required to have separate source documentation and transcribe the data into the eCRF. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 55 | Section 2.0 Study Summary<br>Section 13.2.1 Analysis Sets<br>Section 13.2.2 Analysis of Demographics and Baseline Characteristics<br>Section 13.2.4 Safety Analysis<br>Section 13.2.5 Efficacy Analysis | Analyses will be based on indication (DS or LGS) rather than seizure type and treatment in the antecedent study. | The phrase "by seizure type" is inaccurate. |
| 56 | Section 13.2.1.3 Modified Intent-to-Treat Analysis Set | Clarify that the modified intent-to-treat analysis set only includes subjects who have been assessed for seizures during the treatment period. | The phrase "for seizures" was omitted in the previous protocol versions. |
| 57 | Section 2.0 Study Summary<br>Section 13.2.5 Efficacy Analysis | Specify the statistical methods for efficacy analysis. | Clarification. |
| 58 | Section 13.2.6 Exploratory/Additional Analyses | Provide additional information on exploratory analyses including the proportion of days when rescue ASM is used, optional substudy, CCI [redacted], and palatability/acceptability assessment. | Clarifies the statistical plan for these exploratory endpoints. |
| 59 | Section 13.3.1 Missing or Invalid Data | Clarify that analyses will be based on as-observed data. No imputation will be implemented. | Clarification. |
| 60 | Section 13.3.2 Interim Analyses | Added information on interim analysis (previously indicated no interim analysis.) | Updated plan. |
| 61 | Section 14.1 Study-Site Monitoring Visits | Clarify that monitoring visits can be virtual or on site, as indicated in the clinical monitoring plan. | Keeps the requirement from the protocol and the clinical monitoring plan consistent. |
| 62 | Section 14.2 Protocol Deviations | Require sponsor to assess protocol deviations and assess their impact. | EU CTR requirement. |
| 63 | Section 15.2 Subject Information, Informed Consent, and Subject Authorization | Added justification for inclusion of subjects who cannot provide consent. | EU CTR requirement. |

| Change No. | Sections Affected by Change | Description of Each Change and Rationale | |
|---|---|---|---|
| | ***Location*** | ***Description*** | ***Rationale*** |
| 64 | Section 15.3 Subject Confidentiality | Describe actions to be taken in the event of a serious data breach. | EU CTR requirement. |
| 65 | Appendix A Schedule of Study Procedures | Add a column under Year 4+.<br><br>Separate plasma sample into rows for soticlestat PK and pharmacodynamic samples; remove optional ASM analysis. | Clarifies whether specific procedures should be done at 6- or 12-month intervals.<br><br>Allows fewer samples to be collected, to reduce overall blood volume collected in the study. |
| 66 | Appendix A Schedule of Study Procedures, Part 2 Schedule of Mandatory Safety Phone Calls | Add a separate table on the safety follow-up phone calls during the titration period. | Facilitates follow-up phone calls. |

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## 2.0 STUDY SUMMARY

| | | |
|---|---|---|
| **Name of Sponsor:**<br>Takeda Development Center Americas, Inc. | **Compound:**<br>Soticlestat (TAK-935) | |
| **Title of Protocol:** A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies To Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects With Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2) | **IND No.:** 133627 | **EudraCT No.:**<br>2021-002482-17<br>**EU CT No.:**<br>2022-502802-34-00 |
| **Study Number:** TAK-935-3003 | **Phase:** 3 | |

**Study Design:**

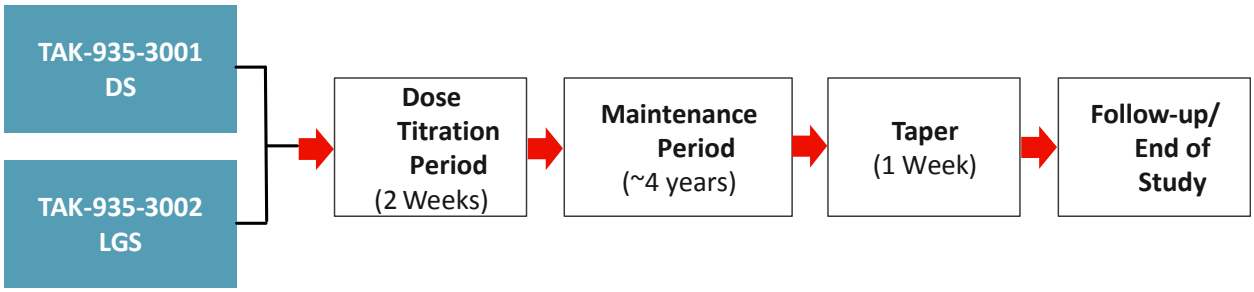
This is a multisite, phase 3, open-label extension (OLE) study designed to obtain additional safety and tolerability data related to soticlestat administered long-term in subjects who participated in an antecedent soticlestat phase 3 clinical study. Additional aims are to assess efficacy in terms of seizure frequency, non–seizure-related symptoms, impact on quality of life, and the pharmacokinetics (PK) and pharmacodynamics (concentration of 24*S*-hydroxycholesterol [24HC]) of soticlestat administration in pediatric and adult subjects with DS or LGS, as well as assessing palatability and acceptability of soticlestat in the pediatric population.

After an initial 2-week titration period (for subjects who roll over from an antecedent double-blind study), the planned treatment duration is approximately 4 years, or until the study is stopped at the discretion of the sponsor, or the product is approved and launched.

The total daily dose of soticlestat will be calculated based on body weight at Visit 1 and given twice daily (BID). Subjects will receive the initial dose of the study drug (200 mg BID adult reference dose, weight-based dosing for weight <45 kg) for the first 7 days of the 14-day dose titration period; the study drug dose will then be increased to the target dose (300 mg BID adult reference dose, weight-based dosing for weight <45 kg). If the subjects do not experience any tolerability issues, they will remain on the target dose for the remaining 7 days of the 14-day titration period, followed by a safety follow-up phone call.

The minimum dose allowed during the study is Dose 1 (for example, 100 mg BID is the minimum dose allowed for subjects weighing ≥45 kg). Subjects who cannot tolerate the minimum dose will be discontinued from the study. The dose may be adjusted every 6 months, depending on the subject's weight. If possible, dose changes due to safety or tolerability may need to be discussed with the medical monitor (ie, from the contract research organization) or the sponsor. Doses between the original dose levels selected for the study may be allowed no more than once after discussing with the sponsor. In the absence of weight change or safety or tolerability considerations, the final dose tolerated by the end of the 2-week titration period should be maintained until the end of the maintenance period. At the end of the maintenance period, whether after the full duration or for early termination, the dose will be tapered for approximately 1 week (unless already at the lowest dose), followed approximately 2 weeks later by a safety follow-up visit or phone call.

The study schematic is shown below.




**Primary Objective:**

To assess the long-term safety and tolerability of soticlestat when administered as adjunctive therapy to standard of care (SOC) (eg, antiseizure medications [ASMs], vagus nerve stimulation, ketogenic diet, or modified Atkins diet) in subjects with DS or LGS.

**Secondary Objectives:**

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

**Subject Population:**

Pediatric and adult subjects with DS or LGS from antecedent soticlestat clinical studies who qualify to roll over to this study.

| | |
|---|---|
| **Number of Subjects:**<br>Approximately 150 subjects with DS and 250 subjects with LGS.<br>Approximately 400 total subjects. | **Number of Sites:**<br>Global, multicenter study to be conducted at approximately 100 sites. |
| **Dose Levels:**<br>300 mg BID (300 mg BID equivalent dose; weight-based dosing for <45 kg) soticlestat | **Route of Administration:**<br>Oral or via enteral feeding tubes. Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted. |
| **Duration of Treatment:**<br>Approximately 4 years, or until the study is stopped at the discretion of the sponsor, or the product is approved and launched. | **Period of Evaluation:**<br>2-week dose titration period for subjects from antecedent double-blind studies.<br>Up to ~4 years maintenance period.<br>~1-week taper period.<br>~2 weeks until safety follow-up. |

**Benefit/Risk Profile:**

The following have been identified as important potential risks and are being closely monitored during the clinical development program:

- Neurological and psychiatric effects (clinical safety data and risks associated with compounds affecting glutamate excitotoxicity).
- Cognitive effects (soticlestat inhibition of neuronal cholesterol-24-hydroxylase and clinical safety data).
- Suicidal ideation or behaviors (class effect of ASMs).
- Cataracts (based on nonclinical data).
- Corrected QT interval prolongation (based on nonclinical data).

In prior studies, soticlestat was generally well tolerated in subjects with developmental epileptic encephalopathies at doses up to 300 mg BID (weight-based dosing for <60 kg).

Given the severe, profound, and chronic nature of DS and LGS, their associated signs and symptoms, and their impact on quality of life, and considering the potential benefits that soticlestat treatment can confer to patients affected by DS or LGS, the benefit-risk profile of soticlestat administration is acceptable for these populations.

**Main Criteria for Inclusion:**

Pediatric and adult subjects with DS or LGS from antecedent soticlestat phase 3 clinical studies; received at least 12 weeks of treatment (combined Titration and Maintenance Periods) with the study drug in the antecedent study; 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; and in the opinion of the investigator, have the potential to benefit from the administration of soticlestat.

**Main Criteria for Exclusion:**

- Unstable, clinically significant neurologic (other than DS or LGS), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, endocrine disease, malignancy including progressive tumors, or other abnormality that may impact the ability to participate in the study or that may potentially confound the study results.
- Abnormal and clinically significant electrocardiogram (ECG) abnormality at Visit 1, including QT interval with Fridericia correction method >450 ms.
- Currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug.
- Considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or has positive answers on item numbers 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1.

**Main Criteria for Evaluation and Analyses:**

The primary endpoints are for safety and include the following:

- Incidence of treatment-emergent AEs.
- Incidence of abnormal values for clinical laboratory tests and ECG evaluations.
- Change from baseline in clinical laboratory test values, vital signs, C-SSRS, and ECG parameters.
- Change from baseline in height and weight for all age groups.
- Absolute value for Tanner stage for children 6 to 17 years of age during the study.
- Absolute values for IGF-1 for children 2 to 17 years of age during the study.

The secondary endpoints include the following:

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

**Statistical Considerations:**

Baseline is the baseline of the antecedent study.

**Safety Analysis Set:** All treated subjects (subjects who take at least 1 dose of study drug) will be included in the safety analysis set. Safety analyses will be based on indication (DS or LGS).

**ITT Analysis Set**: All enrolled subjects will be included in the intent-to-treat (ITT) analysis set. All ITT analyses will be based on indication (DS or LGS).

**mITT Analysis Set:** All enrolled subjects who have received at least 1 dose of study drug and have been assessed for seizures for at least 1 day in the treatment period will be included in the modified ITT (mITT) analysis set. All mITT analyses will be based on indication (DS or LGS).

**Safety Analysis:** Descriptive statistics will be used to summarize all safety endpoints for each indication (DS or LGS). AEs will be summarized using the safety analysis set. All AEs will be coded using Medical Dictionary for Regulatory Activities. Data will be summarized using Preferred Terms and primary System Organ Classes.

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

**Efficacy Analysis:** Efficacy analyses will be performed on the mITT analysis set. The seizure frequency will be calculated for each indication (DS or LGS) based on all data collected during the treatment period. The seizure frequency endpoints will be summarized by indication (DS or LGS) for every 12-week period starting from date of first dose of the study. Distribution-free 2-sided 95% CIs for the median will be provided.

CGI-I, Care GI-I, CGI-I Seizure Intensity and Duration, CGI-I Nonseizure Symptoms, and QI-Disability score will be summarized descriptively for each visit where they were collected and at end of study. The count and percentage of each category/question will be provided by visit. Global impression of improvement scales (CGI-I, Care GI-I, CGI-I Seizure Intensity and Duration, and CGI-I Nonseizure Symptoms) will also be summarized dichotomously in terms of the number and proportion of participants who gave responses of minimally improved or better. Two-sided 95% CIs will be presented for proportions for dichotomous categories.

**Sample Size Justification:** The sample size is determined by the number of subjects who roll over from the antecedent studies (approximately 400 subjects based on the expected enrollment of ongoing antecedent studies). No formal sample size calculation is performed.

# 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 Study-Related Responsibilities template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

## 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

| | |
|---|---|
| 24HC | 24*S*-hydroxycholesterol |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ASM | antiseizure medication |
| AST | aspartate aminotransferase |
| ATC | Anatomic Therapeutic Chemical |
| AUC | area under the plasma concentration-time curve |
| BID | twice daily |
| Care GI-C | Caregiver Global Impression of Change |
| Care GI-I | Caregiver Global Impression of Improvement |
| CCI | [redacted] |
| CGI-C | Clinical Global Impression of Change |
| CGI-I | Clinical Global Impression of Improvement |
| CH24H | cholesterol-24-hydroxylase |
| COVID-19 | coronavirus disease 2019 |
| CRO | contract research organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CTR | Clinical Trials Regulation |
| CYP | cytochrome P450 |
| DEE | developmental epileptic encephalopathy |
| DMC | Data Monitoring Committee |
| DS | Dravet syndrome |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EO | enzyme occupancy |
| CCI | [redacted] |
| CCI | [redacted] |
| EU | European Union |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| G-tube | gastrostomy tube |
| hCG | human chorionic gonadotropin |
| IB | investigator's brochure |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| INR | international normalized ratio |

| | |
|---|---|
| IRB | institutional review board |
| ITT | intent-to-treat |
| IRT | interactive response technology |
| J-tube | jejunostomy tube |
| LFT | liver function test |
| LGS | Lennox-Gastaut syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent-to-treat |
| MMD | major motor drop |
| NG-tube | nasogastric tube |
| OLE | open-label extension |
| PK | pharmacokinetics |
| PTE | pretreatment event |
| QI-Disability | Quality of Life Inventory-Disability |
| QTcF | QT interval with Fridericia correction method |
| rSDV | remote Source Data Verification |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | standard of care |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TESC | The Epilepsy Study Consortium |
| ULN | upper limit of normal |
| US | United States |
| WHO | World Health Organization |



## 3.4 Corporate Identification

| | |
|---|---|
| TDC Japan | Takeda Development Center Japan |
| TDC Asia | Takeda Development Center Asia, Pte Ltd |
| TDC Europe | Takeda Development Centre Europe Ltd. |
| TDC Americas | Takeda Development Center Americas, Inc. |
| TDC | TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable |
| Takeda | TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable |

# 4.0 INTRODUCTION

## 4.1 Background

Dravet syndrome (DS) or severe myoclonic epilepsy in infancy is one of the most well-described disorders of epileptic encephalopathies. Clinically, DS is characterized at onset by frequent convulsive febrile seizures, followed by frequent status epilepticus and nonfebrile seizures that are mainly clonic, unilateral, and of long duration [1].

Lennox-Gastaut syndrome (LGS) is one of the most severe forms of childhood epilepsy. The syndrome usually has its onset between the ages of 1 and 8 years, but occasionally it occurs in children who are older than 8 years, or even into adulthood. LGS includes the presence of multiple seizure types: the hallmark tonic-atonic drop seizures. Other seizure types include atypical absence seizures, but tonic-clonic, myoclonic, and partial seizures are also frequently present.



Soticlestat is a first-in-class small molecule inhibitor of cholesterol-24 hydroxylase (CH24H) in the brain. It is hypothesized that soticlestat treatment will decrease the levels of 24S-hydroxycholesterol (24HC) and improve convulsive seizure control in DS subjects and major motor drop (MMD) seizure control in LGS subjects. Nonclinical studies have demonstrated that soticlestat modulates glutamatergic signaling and significantly reduces spontaneous seizures in murine models of DS. Additional details on the nonclinical program are provided in Section 3 of the current investigator's brochure (IB).

Clinical Study TAK-935-2002 (ELEKTRA) showed efficacy of soticlestat in subjects with DS or LGS. ELEKTRA was a phase 2, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of soticlestat as adjunctive therapy in pediatric subjects aged ≥2 and ≤17 years with LGS or DS. A total of 141 subjects were enrolled (51 with DS and 90 with LGS), and 126 completed the study. Subjects were eligible for enrollment if they demonstrated ≥3 convulsive seizures (in the DS cohort) or ≥4 drop seizures (in the LGS cohort) during a minimum of 4 weeks during the prospective baseline period (based on the seizure diary records), and they were currently on a stable regimen of 1 to 4 concomitant ASMs. This study consisted of 2 main periods, a 4- to 6-week screening/baseline period followed by a 20-week treatment period (8-week titration and dose optimization period and a 12-week maintenance period). Subjects who met the entry criteria were stratified by syndrome and randomized in a 1:1 ratio to soticlestat or matching placebo within each cohort. Subjects were dosed with oral 20 mg or 100 mg soticlestat tablets or matching placebo at 100 mg twice daily (BID) for 1 week, followed by 200 mg BID for another week, before titrating up to 300 mg BID, the maximum allowable dose. Subjects weighing <60 kg were dosed by weight.

In the DS cohort (n = 51), subjects treated with soticlestat demonstrated a 33.8% median reduction in convulsive seizure frequency compared with a 7.0% median increase seen in subjects taking placebo during the 20-week treatment period (median placebo-adjusted reduction in convulsive seizure frequency was 46.0%; p = 0.0007). The responder rate (≥50% reduction in

convulsive seizure frequency compared with baseline) for subjects taking soticlestat in the DS cohort was 30.8% while for placebo was 0%.

In the LGS cohort (n = 88), soticlestat decreased drop seizures by a median of 20.6% as compared with a median decrease of 6% in the placebo group (median placebo-adjusted reduction in drop seizure frequency was 14.8%; p = 0.1279) during the 20-week treatment period. Other secondary endpoints included the Clinical Global Impression of Change (CGI-C) and the Caregiver Global Impression of Change (Care GI-C). For the CGI-C, more soticlestat-treated DS and LGS subjects showed improvement than those receiving placebo (26.9% versus 8% and 27.9% versus 11.1%, respectively) as deemed by the investigator. Caregivers also rated greater improvement in 57.7% and 51.2% of soticlestat-treated DS and LGS subjects compared with 32% and 28.9% of those receiving placebo, respectively, as assessed by the Care GI-C.

In ELEKTRA, soticlestat was generally well tolerated, and safety data were consistent with findings in previous studies. The incidence of treatment-emergent adverse events (TEAEs) was similar in the treatment and placebo groups, with 57 (80.3%) of soticlestat subjects experiencing at least 1 TEAE compared with 52 (74.3%) of placebo subjects. The most common TEAEs in the soticlestat group were upper respiratory tract infection, pyrexia, seizure, nasopharyngitis, decreased appetite, and vomiting. The most frequent TEAEs reported in soticlestat-treated subjects with ≥5% difference from placebo were lethargy and constipation. The incidence of serious TEAEs was similar in both soticlestat and placebo groups, with 11 (15.5%) in the soticlestat group experiencing at least 1 serious TEAE compared with 13 (18.6%) in the placebo group. Four soticlestat (5.6%) subjects discontinued the study compared with 3 in the placebo group (4.3%) due to TEAEs.



An open-label study (TAK-935-18-001, ENDYMION 1) of subjects with developmental epileptic encephalopathies (DEEs) is currently in progress. In addition to ELEKTRA, subjects from other soticlestat phase 1b/2a or 2 studies were eligible to roll over into ENDYMION 1. These include TAK-935-2001, a phase 1b/2a study of soticlestat in a multicenter, randomized, double-blind, placebo controlled, parallel-group, dose-escalation study with an open-label part designed to examine the safety, tolerability, PK, and pharmacodynamics of soticlestat as adjunctive therapy (to antiepileptic drugs) in 18 adult subjects diagnosed with a DEE; TAK-935-18-002, an open-label, parallel-group study in subjects with chromosome 15q duplication (Dup15q) syndrome or cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder demonstrating ≥4 bilateral motor seizures per month.

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

## 4.2 Rationale for the Proposed Study

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 IB), soticlestat is being proposed as adjunctive therapy in pediatric and adult subjects with DS or LGS, highly impacted populations with great unmet need.

This open-label extension (OLE) study is designed to obtain additional safety, tolerability, efficacy, PK, and pharmacodynamic data related to soticlestat administered long-term in subjects who participated in any of the phase 3 clinical studies, including TAK-935-3001 (subjects with DS), or TAK-935-3002 (subjects with LGS) and continue to be treated with standard-of-care (SOC) antiseizure therapy.

No subjects/parents or caregivers were involved in the design of this study.

### 4.3 Benefit/Risk Profile

In the phase 1b/2a TAK-935-2001, phase 2 TAK-935-2002 (ELEKTRA), and open-label pilot TAK-935-18-002 (ARCADE) studies, the safety and tolerability data indicate that soticlestat was generally well tolerated in subjects with DEEs at doses up to 300 mg BID (weight-based dosing for <60 kg).

The following have been identified as important potential risks and are being closely monitored during the clinical development program:

- Neurological and psychiatric effects (clinical safety data and risks associated with compounds affecting glutamate excitotoxicity).
- Cognitive effects (soticlestat inhibition of neuronal CH24H and clinical safety data).
- Suicidal ideation or behaviors (class effect of ASMs).
- Cataracts (based on nonclinical data).
- Corrected QT interval prolongation (based on nonclinical data).



In addition, on the basis of nonclinical studies, soticlestat is considered unlikely to cause human teratogenicity/fetotoxicity in early pregnancy. In the definitive fertility and embryo-fetal development studies in rats and rabbits with soticlestat, there was no evidence of teratogenicity at any dose up to 2000 mg/kg/d in rats (NCDS-02519) and 400 mg/kg/d in rabbits (NCDS-02518), respectively, which was associated with exposures ≥95 times higher than the $AUC_{24}$ (area under the plasma concentration-time curve from 0 to 24 hours) of the maximum recommended human dose of 300 mg BID per day.

More information about the known and expected benefits and reasonably anticipated AEs of soticlestat may be found in the current edition of the IB. This study will further examine risk and establish benefit in DS and LGS subjects.

DS is characterized by treatment-resistant seizures, presenting at a very young age. In addition, mortality is especially high in DS (up to 21%) [2], even compared with other epilepsy syndromes, with a 30-fold higher rate of sudden unexpected death in epilepsy (SUDEP) that accounts for up to 60% of deaths in these patients [3]. Given the severe, profound, and chronic nature of DS and its associated signs and symptoms and their impact on quality of life, and considering the potential benefits that soticlestat treatment can confer to patients affected by DS, the benefit-risk profile of soticlestat administration is acceptable for this population.

LGS is characterized by multiple treatment-resistant seizure types, abnormal electroencephalogram, and intellectual impairment. Given the severe, profound, and chronic nature of LGS, its impact on quality of life, and its associated signs and symptoms, and considering the potential benefits that can be conferred to patients affected by LGS, the benefit-risk profile of soticlestat administration is acceptable for this population.

# 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 SOC (eg, ASMs, vagus nerve stimulation, ketogenic diet, modified Atkins diet) in subjects with DS or LGS.



### 5.1.2 Secondary Objectives

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

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

### 5.1.3 Exploratory Objectives

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

- [redacted] CCI [redacted]
- Days when rescue ASMs are used.
- [redacted] CCI [redacted].

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

[redacted] CCI [redacted].

## 5.2 Endpoints

Baseline definitions can be found in Section 13.2.5.

### 5.2.1 Primary Endpoints—Safety

The primary endpoints include the following:

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



### 5.2.2 Secondary Endpoints

The secondary endpoints include the following:

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

### 5.2.3 Exploratory Endpoints

The exploratory endpoints include the following:

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

## 6.0 STUDY DESIGN AND DESCRIPTION

### 6.1 Study Design

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

Subjects will be eligible to enroll in this study if they have received at least 12 weeks of treatment (combined Titration and Maintenance Period) with the study drug in an antecedent phase 3 study and do not have a serious or severe AE that, in the investigator's or sponsor's opinion, was related to the study drug and would make it unsafe for the patient to continue receiving the study drug.

Approximately 400 male and female pediatric and adult subjects from antecedent phase 3 studies will be rolled over into this study, approximately 150 subjects with DS and 250 subjects with LGS. Most of the assessments from the prospective baseline of the antecedent study will be used as baseline for this study. However, in the event that there is a treatment gap between the antecedent study and this study (ie, subject cannot roll over immediately), such assessments must

be repeated at Visit 1 of this study if the treatment gap is more than 21 days. The identity of the treatment received during the antecedent study will remain blinded.

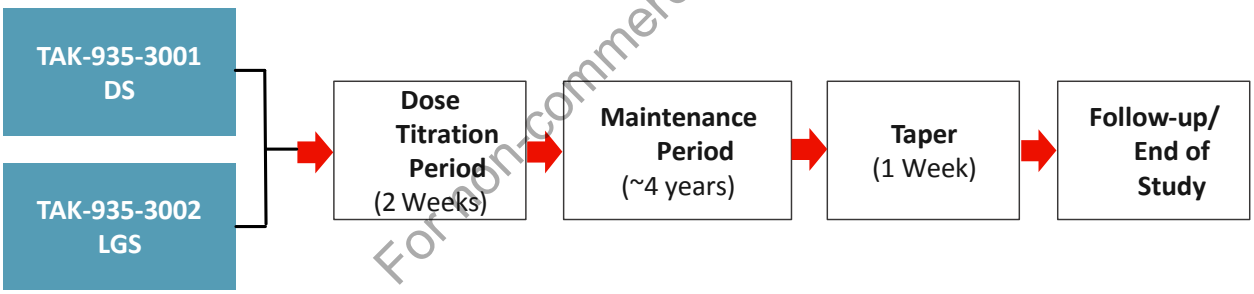
After an initial 2-week titration period (for subjects who roll over from an antecedent double-blind study), the planned treatment duration is approximately 4 years, or until the study is stopped at the discretion of the sponsor, or the product is approved and launched. Subjects who complete the full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

Soticlestat added to current antiseizure therapy will be administered orally BID with or without food or via enteral feeding tubes including but not limited to nasogastric (NG)-tube, gastrostomy tube (G-tube), or MIC-KEY button. A jejunostomy tube (J-tube) may be considered following approval by the medical monitor (ie, from the contract research organization [CRO]) or sponsor. Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.

A schematic of the study design is shown in Figure 6.a. A schedule of assessments is listed in Appendix A.



**Figure 6.a Schematic of Study Design**




DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome.

The total daily dose of soticlestat will be calculated based on body weight at Visit 1 and given BID. Subjects from TAK-935-3001 and TAK-935-3002 will receive Dose 2, the initial dose of study drug (200 mg BID adult reference dose, weight-based dosing for weight <45 kg) for the first 7 days, then study drug dose will be increased to the target dose, Dose 3 (300 mg BID adult reference dose, weight-based dosing for weight <45 kg). If the subjects do not experience any tolerability issues, they will remain on Dose 3 for the remaining 7 days of the titration period, followed by a safety follow-up phone call.

The dosing schedules by weight are shown in Table 6.a through Table 6.d. The minimum dose allowed during the study is Dose 1 (for example, 100 mg BID is the minimum dose allowed for subjects weighing ≥45 kg). Subjects who cannot tolerate the minimum dose will be discontinued from the study. Subjects weighing <45 kg will be dispensed 20 mg mini-tablets for the titration period followed by 20 mg mini-tablets or 100 mg tablets for the maintenance period. Subjects weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets. The dose may be

adjusted every 6 months, depending on the subject's weight. Doses between the original dose levels selected for the study may be allowed based on tolerability but no more than once during the study, after discussing with the sponsor. The recommended doses between the original dose levels selected for the study are listed in Table 6.e.

**Table 6.a Dosing Schedules by Weight, 10 to <15 kg**

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

BID: twice daily; No.: number.

**Table 6.b Dosing Schedules by Weight, 15 to <30 kg**

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

BID: twice daily; No.: number.

**Table 6.c Dosing Schedules by Weight, 30 to <45 kg**

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

BID: twice daily; No.: number.

**Table 6.d Dosing Schedules by Weight, ≥45 kg**

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

BID: twice daily; No.: number.

**Table 6.e Recommended Intermediate Doses Between Scheduled Dose Levels for Each Weight Band**

| | Recommended Intermediate Dose Between Dose 1 and Dose 2 | | Recommended Intermediate Dose Between Dose 2 and Dose 3 | |
|---|---|---|---|---|
| Weight | Soticlestat (mg/dose) | Number Tablets or Mini-tablets | Soticlestat (mg/dose) | Number Tablets or Mini-tablets |
| 10 to <15 kg | NA | NA | 80 mg BID | 4 mini-tablets BID |
| 15 to <30 kg | 80 mg BID | 4 mini-tablets BID | 160 mg BID | 8 mini-tablets BID |
| 30 to <45kg | 100 mg BID | 5 mini-tablets BID OR 1 tablet BID | 160 mg BID | 8 mini-tablets BID |
| ≥45 kg | 140 mg BID | 7 mini-tablets BID | 240 mg BID | 12 mini-tablets BID |

BID: twice daily; NA: not applicable.



### 6.1.1 Dose Titration Period (2 Weeks)

Subjects from double-blind studies will receive soticlestat Dose 2 for their weight (Table 6.a through Table 6.d) for the first 7 days after Visit 1; a safety follow-up call will be made within 2 days of the first dose. There will be another safety follow-up phone call or onsite visit at Day 7 (Visit 2). Study drug dose will then be increased to Dose 3 for 7 days; safety follow-up phone calls will again be made within 2 days of the first dose on the new amount and at the end of the 14-day titration period.

A decrease in dose level (to Dose 2 or Dose 1) is allowed during the titration period if required for safety and tolerability. Doses between the scheduled dose levels may be allowed after discussing with the sponsor (the recommend doses are listed in Table 6.e). Subjects who cannot tolerate Dose 1 for their weight band will be discontinued from treatment. The maximum allowed dose is 300 mg BID. The final dose tolerated by the end of the 2-week titration period should be maintained until the end of the maintenance period, unless tolerability issues arise.

### 6.1.2 Maintenance Period

In the absence of weight change or safety or tolerability considerations, the final dose tolerated by the end of the 2-week titration period should be maintained until the end of the maintenance period. However, during the maintenance period, the dose may be decreased by 1 dose level to the previous lower dose, for safety and tolerability issues. For example, Dose 3 may be reduced to Dose 2, and Dose 2 may be reduced to Dose 1. The minimum dose is Dose 1 (100 mg BID adult reference dose; or weight-based equivalent dosing for <45 kg); subjects who cannot tolerate the minimum dose (Dose 1) will be discontinued from treatment. Doses between the scheduled dose levels may be allowed after discussing with the sponsor (the recommend doses are listed in Table 6.e). The dose may be adjusted every 6 months, depending on the subject's weight.

As the duration of this study is expected to expand for about 4 years, it is anticipated that the dosing could be interrupted unexpectedly for a relatively long time (including but not limited to coronavirus disease 2019 [COVID-19] lockdown, natural disasters, AEs unrelated to the study drug that prohibit enteral dosing). In such extenuating cases, whether the subject should resume dosing, retitrate, or discontinue after the situation improves and whether certain study procedures need to be repeated during an unscheduled visit to ensure the safety of the subject, will depend on the investigator's discretion, and the risk/benefit judgement should be clearly documented. To keep consistency of practice among sites, the sponsor or the medical monitor should be consulted before the subject resumes the original dosing or retitrates.



### 6.1.3 Study Discontinuation/Completion

At the end of the maintenance period, whether after the full duration or for early termination, the dose will be tapered for approximately 1 week (unless already at the lowest dose). During the taper period, the study drug dose will be tapered down to a lower dose (taper Dose 3 to Dose 2, taper Dose 2 to Dose 1) no more frequently than every 3 days until the study drug is discontinued. After tapering, the subject/caregiver will complete a safety follow-up phone call (or visit) approximately 2 weeks after the last dose of study drug and exit from the study.

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

### 6.1.4 Overall Schedule of Study Assessments

The schedule of assessments is presented by visit in Appendix A and study assessment methods are presented in Section 9.1. The baseline visit (Visit 1) can occur on the same day as the end-of-treatment visit of the antecedent study. If these 2 visits are on different days, collection of concomitant medication, serum pregnancy test, C-SSRS, and ECG should be repeated on Visit 1. Other identical safety assessments (weight, height, vital signs, physical examination, neurological examination, ophthalmological examination, hematology and serum chemistry, urinalysis) and quality of life assessments taken at the subject's last visit of the antecedent study do not need to be repeated if performed within 21 days before Visit 1, but could be performed at

the discretion of the investigator. After Visit 1, subsequent visits will occur at Week 1 (Day 7), 4, 13, 26, 39, 52 (all in Year 1); every 13 weeks starting with Week 65 in Year 2; every 26 weeks starting with Week 130 in Year 3. Subjects rolling-over from prior open-label phase 3 studies can directly start from the maintenance period, and the treatment period in the antecedent study will be counted into the maintenance period of this study (for example, if the treatment period in the antecedent study is 1 year, the subjects will start from Year 2 after rolling over to this study).

In jurisdictions where home visits by site staff in clinical trials are allowed, these may be used as an alternative to study visits. In special cases when subjects or parents/caregivers may have difficulties with travel for clinic visits, (such as COVID-19 restrictions or other extenuating circumstances), virtual visits are allowed, except for Visit 1. In such cases, study procedures related to safety assessments should be completed locally when possible. Please refer to Appendix C for detailed information. Scheduled virtual visits could also be conducted as onsite visits, if judged necessary by the subjects, parents/caregivers, or the investigators.

Safety, efficacy, and exploratory assessments will be performed at scheduled visits throughout the treatment period. AEs and concomitant medications will be monitored continuously throughout the study. Blood samples will be collected for soticlestat PK and 24HC analysis.



## 6.2 Justification for Study Design, Dose, and Endpoints

### 6.2.1 Study Design

This OLE study will enroll subjects from soticlestat phase 3 clinical studies. Subjects should receive at least 12 weeks of treatment (combined Titration and Maintenance Periods) with the study drug in the antecedent study. It will obtain additional safety and tolerability data related to soticlestat administered long-term in these subjects. It will also provide data on the long-term efficacy of soticlestat as measured by seizure frequency and global impression scales, as well as long-term data on PK, pharmacodynamics, and caregiver-completed measures of quality-of-life, caregiver burden, and subject and caregiver study experience (the latter at selected sites only). Data on palatability and acceptability of soticlestat in pediatric subjects will also be collected.

The treatment in antecedent double-blind studies will remain blinded. All subjects from antecedent double-blind studies will start with Dose 2 and may be titrated to Dose 3 (the target dose) to ensure that subjects previously on placebo do not have an abrupt transition to soticlestat.

### 6.2.2 Endpoints

This study will use most of the same endpoints as the antecedent studies. In this open-label study, safety endpoints will be primary, efficacy secondary. Palatability and acceptability in pediatric subjects will be assessed as exploratory endpoints.

### 6.2.3 Dose

Dose selection is based on a comprehensive analysis of the safety, tolerability, PK, and pharmacodynamic data from 4 completed single- and multiple-dose phase 1 studies in healthy subjects; the safety, tolerability, and PK data from the phase 1b/2a study of soticlestat as

adjunctive therapy in adult subjects with DEEs; and the efficacy, safety, PK, and pharmacodynamic data in the ELEKTRA study in pediatric subjects with DS or LGS, where the same target dose of 300 mg BID (weight-based equivalent in pediatrics) demonstrated statistically significant and clinically meaningful seizure reduction in DS subjects, and numerical seizure frequency reduction in subjects with LGS, while maintaining a favorable safety and tolerability profile.

The efficacy of soticlestat is related to CH24H inhibition and a decrease in 24HC levels in humans. The extent of CH24H inhibition required for efficacy was estimated in an animal model of epilepsy. In a mouse pentylenetetrazol-induced kindling development model, effects of soticlestat on seizure severity were associated with the degree of CH24H inhibition [4]. A 75% reduction in the severity score was associated with 90% reduction in brain 24HC levels. The minimum required 24HC lowering for efficacy was approximately 60%, yielding 40% decrease in the severity score. The 24HC lowering effect was then converted into 65% of the CH24H enzyme occupancy (EO) rate, using a model established in mice (Target occupancy evaluation for CH24H inhibitor, soticlestat, with liquid chromatography/tandem mass spectrometry. Report number:16354). In summary, these nonclinical pharmacology studies suggest that high degree of target occupancy (≥65%) and 24HC reduction (≥60%) are considered to be related to the efficacy in the nonclinical animal model.

The target dose of 300 mg BID (weight-based equivalent in pediatrics) will achieve the degree of target occupancy and 24HC reduction required for efficacy. Based on a population PK/ pharmacodynamics/EO model using data from 4 phase 1 studies in healthy subjects, the phase 1b/2a study in adult subjects with DEEs, and the TAK-935-2002 (ELEKTRA) study in pediatric subjects with DS or LGS, the 300 mg BID dose (weight-based equivalent in pediatrics) is estimated to achieve approximately 90% EO with approximately 82% decrease in 24HC level and potentially resulting in efficacy.



In addition, the same soticlestat target dose of 300 mg BID (adult reference dose; weight-based equivalent dosing for <60 kg) was administered in ELEKTRA and demonstrated clinically meaningful seizure reduction in DS and LGS subjects while maintaining a favorable safety and tolerability profile. Approximately 79% of subjects in the double-blind, randomized, placebo-controlled ELEKTRA study were able to be titrated up to and maintained on 300 mg BID (or adult weight-based equivalent) until the end of the maintenance period.

Soticlestat-treated subjects with DS reported a 33.8% median reduction in convulsive seizures while those subjects receiving placebo experienced a median increase of 7.0% in convulsive seizures (median placebo-adjusted reduction in seizure frequency was 46.0%; $p = 0.0007$) over the 20-week treatment period. Responder rates (≥50% reduction in convulsive seizure frequency compared with baseline) for soticlestat-treated subjects with DS were 30.8% versus 0% in placebo, respectively.

Soticlestat-treated subjects with LGS reported a 20.6% median reduction in drop seizures while those subjects receiving placebo experienced a median decrease of 6% in drop seizures (median placebo-adjusted reduction in seizure frequency was 14.8%) over the 20-week treatment period.

Responder rates (≥50% reduction in drop seizure frequency compared with baseline) for soticlestat-treated subjects with LGS were 16.3% versus 13.3% in placebo, respectively.

Soticlestat was generally safe and well tolerated at this dose in this study, and safety was consistent with previous studies with no new signals identified. The incidence of TEAEs was similar between the DS and LGS strata compared with placebo with 57 soticlestat subjects (80.3%) experiencing at least 1 TEAE compared with 52 placebo subjects (74.3%). The most frequent TEAEs reported in soticlestat-treated subjects with ≥5% difference from placebo were lethargy and constipation. The incidence of serious adverse events (SAEs) was similar in both soticlestat and placebo groups, with 11 (15.5%) in the soticlestat group experiencing at least 1 treatment-emergent SAE compared with 13 (18.6%) in the placebo group. There were no deaths reported. The combination of clinically meaningful convulsive seizure reduction and favorable tolerability and safety profile in ELEKTRA support the selection of 300 mg BID as the soticlestat target dose (adult reference dose; weight-based equivalent dosing for <45 kg BID).

The weight-based equivalent dosing in pediatrics was determined using the population PK model. Simulations were conducted using body weight intervals of 1 kg, dose strengths from 40 to 300 mg using 20 mg mini-tablets and 100 mg tablets, and a BID dosing regimen. A total of 10,000 simulations of steady-state exposure (median area under the plasma concentration-time curve [AUC]) were performed. A threshold for the fraction of subjects at or above the reference value was set to 35%. Setting the percentage threshold at "35%" ensures the safety of pediatric subjects as the reference AUC values are median steady-state AUC values in adults, ie, 50% of the adult population has AUCs above the reference AUC values while no more than 35% of pediatric population will have AUCs above the reference AUC values). Furthermore, an effort has been made to keep pediatric exposure from exceeding the 90th percentile of the adult exposure. The resulting weight-based equivalent dosing in pediatrics is provided in Table 6.a through Table 6.d.



## 6.3 Premature Termination or Suspension of Study or Study Site

### 6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for soticlestat, such that the benefit-risk is no longer acceptable for subjects participating in the study.
- The Data Monitoring Committee (DMC) recommends that the study should be suspended or terminated.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

### 6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or is otherwise permitted by the contractual agreement.

### 6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

### 6.3.4 Duration of an Individual Subject's Study Participation

Individual subjects will participate in the study for approximately 4 years, or until the study is stopped at the discretion of the sponsor, or the product is approved and launched.

### 6.3.5 End of Study/Study Completion 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.

### 6.3.6 Total Study Duration

It is anticipated that this study will last approximately 4 years, or until the study is stopped at the discretion of the sponsor, or the product is approved and launched.



## 6.4 Poststudy Access

Study drug may be available upon completion of the subject's participation in the study, as the study is planned to continue until soticlestat is approved and launched. The subject should be returned to the care of a physician and standard therapies initiated or resumed as required.

# 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria need to be confirmed before the first dose.

## 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. Subject must have:
    - Been previously enrolled in a phase 3 soticlestat clinical study.

- Received at least 12 weeks of treatment (combined Titration and Maintenance Periods) with the study drug in the antecedent study and not have a serious or severe AE that, in the investigator's or sponsor's opinion, was related to the study drug and would make it unsafe for the patient to continue receiving the study drug.

2. In the opinion of the investigator, the subject has the potential to benefit from the administration of soticlestat.
3. In the opinion of the investigator, the subject and/or the subject's parent or legal guardian or caregiver is capable of understanding and complying with protocol requirements including completion of appropriate assessments, maintaining an accurate and complete daily seizure diary, and taking study drug for the duration of the study.

   If the subject is living in a residential facility, a minimally possible number of staff member(s) at the facility who are the subject's primary caretaker(s) may be identified as caregivers who (per investigator's judgment) are capable of complying with protocol requirements as indicated above.
4. The subject or the subject's parent or legal guardian is willing and able to read, understand, and sign and date an informed consent form (ICF), assent form (if applicable), and any required privacy authorization before the initiation of any study procedures.
5. Female subjects of childbearing potential (defined as first menarche) must have a negative pregnancy test and agree to use an effective (not applicable for Germany) or highly effective method of birth control during the study and for 30 days following the last dose of study drug.

   Effective contraceptive methods include the following (not applicable for Germany):

   - Double-barrier method (contraceptive sponge, diaphragm, or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action, PLUS condom with or without spermicide.

   Highly effective contraceptive methods include the following:

   - Nonhormonal methods:
     - Intrauterine device.
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).
     - Sexual abstinence: Sexual abstinence may be considered as a method only if defined as refraining from heterosexual intercourse and determined to be the usual lifestyle before entering the study with reliability of abstinence for the duration of the study participation and for 30 days after last dose of study drug.

- Hormonal methods:

  – Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation, initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months.

  – Progestogen-only hormonal contraception associated with inhibition of ovulation, initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter until she has been on the contraceptive for 3 months.

## 7.2 Exclusion Criteria

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

1. Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, endocrine disease, malignancy including progressive tumors, or other abnormality that may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the medical monitor may be warranted.
2. Abnormal and clinically significant ECG abnormality at Visit 1 including QT interval with Fridericia correction method (QTcF) >450 ms confirmed with a repeat ECG using manual measurement of QTcF. Clinically significant ECG abnormalities should be discussed with the medical monitor.
3. Subject is currently pregnant or breastfeeding or is planning to become pregnant during the study or within 30 days of the last dose of study drug.
4. Subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property. Subjects who have positive answers on item numbers 4 or 5 on the C-SSRS before dosing are excluded. This scale will only be administered to subjects aged ≥6 years.



## 7.3 Excluded Medications

Strong cytochrome P450 (CYP)3A inducers are excluded from before dosing until the end of the follow-up visit, except for ASMs (eg, carbamazepine, phenobarbital, phenytoin) and topical preparations; refer to Appendix B for examples.

Vaccinations are allowed; however, the medical monitor should be informed about changes in the subject's vaccination status and document it under the concomitant medication section of the eCRF.

The use of felbamate is only allowed in this study if the subject was on felbamate in the antecedent study (as per the antecedent study criteria).

Subjects are instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

All medications, including vitamin supplements, over-the-counter medications, herbal preparations, and artisanal cannabidiol will be collected throughout the study and documented under the concomitant medication section of the eCRF.

## 7.4 Diet, Fluid, and Activity Control

As the effect of a strong CYP3A4 inhibitor on the PK of soticlestat is small (<25%), consumption of the fruit and juice of grapefruit, Seville oranges, and starfruit is permitted.

## 7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the eCRF using the categories detailed in this section.

Study subjects will be withdrawn from the study/study drug for the following reasons:

1. Failure to meet continuation criteria: Enrollment in any other clinical study involving an investigational product or enrollment in any other type of clinical trial judged not to be scientifically or medically compatible with this study.
2. Withdrawal by investigator: The investigator decides that the subject should be discontinued from the study. (Note: The specific reason for discontinuation must be recorded in the eCRF, therefore "withdrawal by investigator" may only to be used if no other pertinent reason for discontinuation is applicable).
3. Withdrawal by subject/parent or legal guardian (Note: The specific reason for discontinuation should be recorded in the eCRF, therefore "withdrawal by subject/parent or legal guardian" may 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 a TEAE should not be recorded in this category. Similarly, lack of efficacy should not be recorded in this category.
4. Sponsor decision:
   a) The sponsor or its designee discontinues the study.
   b) The sponsor or its designee discontinues the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
   c) The sponsor or its designee stops the clinical study at a particular site.
5. Discontinuation due to AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the AE.

If the investigator decides that the subject should be withdrawn because of an AE 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.

a) Liver function test (LFT) abnormalities: Study drug should be discontinued immediately (withdrawal of the subject from the study should be discussed with the sponsor or medical monitor) with appropriate clinical follow-up, including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status (see Section 9.3.1) if the following circumstances occur at any time during study drug treatment:

   i. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 times the upper limit of normal (ULN), or

   ii. Serum ALT or AST persistently >5 times the ULN that persists for more than 2 weeks, or

   iii. Serum ALT or AST >3 times the ULN in conjunction with elevated total bilirubin >2 times the ULN or international normalized ratio (INR) >1.5, or

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

b) QTcF >500 ms or an increase of QTcF >60 msec above baseline.

   Note: Study drug should be discontinued immediately (withdrawal of the subject from the study should be discussed with the sponsor or medical monitor) with appropriate clinical follow-up and confirmation by repeat ECG with manual measurement of the QTcF interval if the QTcF is >500 ms or if there is an increase of QTcF >60 msec above baseline.

c) Greater than a 100% increase in 28-day seizure frequency from the 4- to 6-week prospective baseline period of the antecedent study, and considered by the investigator to be clinically significant worsening of the seizure frequency that is related to the study drug.

d) Not tolerating the lowest dose of the study drug.

e) Suicidal ideation: Subjects who experience suicidal ideation or who attempt suicide will be immediately withdrawn from the study.

6. Lost to follow-up: The subject did not attend visits, and multiple attempts to contact the subjects were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.

7. Pregnancy: Female subject of childbearing potential is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.18.

8. Coronavirus disease 2019 (COVID-19)/pandemic: If, in the opinion of the investigator, the safety of a trial 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.
9. Noncompliance with study drug or noncompliance with completion of the seizure diary or other study-related procedures.
10. Significant protocol deviation: The discovery following soticlestat dosing that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and/or continued participation poses an unacceptable risk to the subject's health.
11. Lack of efficacy.
12. Other: The specific reason should be recorded in the eCRF.

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).



### 7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

## 8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

### 8.1 Study Drug and Materials

The investigational product for this study is soticlestat, as described in Table 8.a.

**Table 8.a Study Interventions Administered**

| | |
|---|---|
| **Intervention Label** | Soticlestat |
| **Intervention Name** | Soticlestat |
| **Former Name(s) or Alias(es)** | TAK-935 |
| **Intervention Description** | Soticlestat is a white to nearly white powder or crystal. Soticlestat is nonhygroscopic [redacted] |
| **Excipients** | Excipients are detailed in the current investigator's brochure |
| **Type** | Drug |
| **Dose Formulation** | Mini-tablets and tablets |
| **Unit Dose Strength(s)** | 20 mg mini-tablets or 100 mg tablets |
| **Dosage Level(s)** | BID administration as shown in Table 6.a through Table 6.d |
| **Route of Administration** | Orally BID with or without food or via enteral feeding tubes including but not limited to NG-tube, G-tube, low-profile gastric tube (MIC-KEY button). A J-tube may be considered following approval by the medical monitor or sponsor. [a] |
| **Use** | Experimental |
| **Classification** | IMP |
| **Authorization Status** | Not authorized in any country |
| **Sourcing** | Provided centrally by the sponsor |
| **Packaging and Labeling** | Study drug will be supplied in high-density polyethylene bottles with induction seal and child-resistant caps. Each bottle will contain a label that includes pertinent study information and caution statements. |

BID: twice daily; G-tube: gastrostomy tube; IMP: investigational medicinal product; J-tube: jejunostomy tube; NG: nasogastric.
[a] Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.



There is no auxiliary medicinal product in this study.

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term "study drug" refers to all or any of the drugs defined below.

#### *8.1.1.1 Study Drug*

The sponsor will supply the study sites with soticlestat 20 mg mini-tablets and soticlestat 100 mg tablets. Study drug will be supplied in high-density polyethylene bottles with induction seal and child-resistant caps. Each bottle will contain a label that includes pertinent study information and caution statements.

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

Changes to sponsor-supplied packaging, including the addition of labels before dosing, may not be made without full agreement in advance by the sponsor. Such additional labels (eg, those used

when dispensing marketed product) may, on a case-by-case basis, be applied to the study intervention to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study participant by name.

The label shall also include a batch identifier and medication identification number to allow for traceability of the study drug via interactive response technology (IRT).

All subjects will continue on SOC antiseizure therapies throughout the study (not provided by the sponsor).

#### *8.1.1.2 Rescue Medication*

Rescue ASMs as per SOC will be allowed throughout the study and their use recorded in the daily seizure and medication diary. Rescue medication will not be supplied by the sponsor.



### 8.1.2 Storage

Study drug must be kept in an appropriate, temperature-controlled, limited-access, secure place until it is dispensed, destroyed by the site (if approved by sponsor or designee), 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.

### 8.1.3 Dose and Regimen

This study involves open-label administration of soticlestat (weight-based dosing) BID. Weight-based doses and the regimens for titration, increase, and decrease of dose at each weight are specified in Table 6.a through Table 6.d.

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

- Explaining the correct use of the study drug to the subject/parent or caregiver.
- Verifying that instructions are followed properly.
- Maintaining accurate records of study drug dispensing and collection.
- Destroying locally at site (if approved by sponsor or designee) or returning all unused study drugs to the sponsor or its designee at the end of the study after the monitor completes final accountability and reconciliation.

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

All study drug provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the study drug will be fully documented and verified by a second person. Detailed records of the amounts of the study drug received, dispensed, and remaining at the end of the study will be maintained.

Soticlestat added to current antiseizure therapy will be administered BID orally with or without food or via enteral feeding tubes including but not limited to NG-tube, G-tube, or MIC-KEY button. A J-tube may be considered following approval by the medical monitor or sponsor.

Subject/parent or caregiver will be instructed to contact the investigator as soon as possible if the subject has a complaint or problem with the study drug so that the situation can be assessed.

Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.

The study site personnel will indicate how many tablets/mini-tablets should be taken per day in a separate dosing instruction. See Section 6.1.1 for a detailed description of the titration scheme.

Tablets/mini-tablets may be crushed and mixed well in applesauce, yogurt, or other liquid of similar consistency before dosing. The amount of applesauce, yogurt, or other liquid of similar consistency needed is dependent upon the number of tablets/mini-tablets the subject is taking. Approximately one-half teaspoon or 2.5 mL of applesauce or yogurt or other liquid of similar consistency is needed for each mini-tablet taken, and 2 teaspoons or 10 mL are needed for each tablet taken.



For subjects receiving study drug via enteral feeding tubes, study drug will be crushed and suspended in water, and the suspension will be administered via the feeding tubes. Complete instructions for enteral feeding tubes will be provided to the subject/parent or caregiver. Other medications or enteral feeds should not be given concurrently with the study drug.

Soticlestat tablets should be administered at approximately the same times each day. The actual date, time, and dose of study drug administrations before PK sample collection will be recorded. The actual date and time of all PK sample collections will also be recorded.

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/parent or caregiver remembers after 4 hours of the scheduled time of dosing, the dosing should be skipped and reported as a missed dose in their daily seizure and medication diary and on the next clinic visit.

The planned daily dose and tablet count to be administered to subjects during the titration period is shown in Section 6.1. During the titration period, 2 days after each dose escalation or taper, the subject/parent or caregiver will be contacted by phone (safety check phone call) to monitor study drug compliance, to assess the tolerability and safety of the study drug, and to monitor concomitant medication use and TEAEs.

Subject/parent or caregiver should return unused study drug at each study visit to allow the investigator or designee to evaluate subject's compliance with the dosing instructions.

### 8.1.4 Dose Tapering

During the tapering period of approximately 1 week following the last maintenance visit, the soticlestat dose will be tapered down to a lower dose no more frequently than every 3 days based on the investigator's discretion until soticlestat is discontinued. After tapering, patients will complete a safety follow-up visit or phone call approximately 2 weeks after the last dose of study drug and exit the study.

### 8.1.5 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at doses above that is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated TEAEs) will be documented on an Overdose page of the eCRF to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered TEAEs. TEAEs associated with an overdose will be documented on AE eCRFs according to Section 10.2.1.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically, as determined by the investigator.



## 8.2 Blinding

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

## 8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies, including the number of returned tablets to sites, will be counted and reconciled at the site before being destroyed locally by the site (if approved by sponsor or designee) or returned to the sponsor or designee.

The investigator or designee must ensure that the study drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. The investigator or designee is responsible for ensuring that the study drug provided to the subject and returned from the subject is accounted for and noted in source documents. To document appropriate use of study drug, the investigator or designee must maintain records of all study drug delivery to the site, site inventory, dispensation and use by each subject, destruction by the site (if approved by sponsor or designee), and return to the sponsor or designee. If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Periodically, throughout and at the conclusion of the study, the monitor or a sponsor representative will conduct an inventory of unused study drug. At the completion of the study, a final study drug accountability review will be conducted before the unused study drugs are destroyed by the site (if approved by sponsor or designee) or returned to the sponsor or its designee for destruction. All study drug not returned to the site by a subject must be investigated by the site and appropriately documented. 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.

Destruction at the site, where applicable, must be in accordance with local standard practice with prior approval from the sponsor or CRO.

The site must have destruction procedures in place and be able to supply a Certificate of Destruction or similar document once destruction is completed. Sites shall also document the event in the IRT.



# 9.0 STUDY PLAN

## 9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The schedule of study procedures is located in Appendix A.

### 9.1.1 Informed Consent Procedure

Informed written consent must be obtained before the subject enters into the study and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

The investigational site is responsible for the consenting process. The requirements of informed consent are described in Section 15.2.

Providing a blood sample for genetic testing is optional for this study. (Genetic samples will not be collected in China, France, or Brazil.) A separate informed consent form pertaining to collection, storage, and analysis of the sample must be obtained before collecting the sample. The provision of consent to collect and analyze the sample for genetic testing is independent of consent to the other aspects of the study.

A subset of caregivers recruited at selected clinical sites will also be asked to provide qualitative input about the caregiver's and subject's study experience over the course of the OLE study. Participation is optional, and a decision not to participate will have no impact on the subject's study eligibility or enrollment. A separate ICF pertaining to the collection, storage, and analysis of caregiver input data will be obtained before data collection. The provision of consent to collect and analyze caregiver input data is independent of consent to other aspects of the study.

### 9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information will be obtained from the data collected in the antecedent study.

Medical history will be obtained from the data collected in the antecedent study. In addition, medication started and stopped during the antecedent study will be collected. TEAEs from the antecedent study that are still ongoing at the time of consent for this study will be captured as medical history.

### 9.1.3 Concomitant Medications and Nonpharmacologic Therapies and Procedures

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

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

The list of excluded medications is provided in Section 7.3.



### 9.1.4 Vital Sign, Height, And Weight Procedures

The following vital signs, as well as height and weight, will be recorded at the times specified in Appendix A: systolic and diastolic blood pressure (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), temperature (°C or °F), height (cm), weight (kg). If clinically significant vital sign changes from baseline are noted, the changes will be documented as AEs in the AE eCRF. Baseline events will be documented in the medical history eCRF. Clinical significance is defined as any variation in vital signs that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

Weight and height 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 caregiver). The investigator must record in the source document the reason for not obtaining height or weight (eg, the subject is in a wheelchair).

### 9.1.5 Physical Examination Procedure

A physical examination will be performed at the times specified in Appendix A. The following assessments will be completed as much as possible during each examination: eyes; ears; nose; throat; cardiovascular system; respiratory system; gastrointestinal system; dermatologic system; musculoskeletal system; extremities; nervous system; lymph nodes; and other. If certain

assessments could not be completed due to the subject's inability to cooperate, the reason should be documented.

If clinically significant changes from baseline are noted, the changes will be documented as TEAEs in the AE eCRF. Baseline events will be documented in the medical history eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

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

### 9.1.6 Neurological Examination Procedure

A separate neurological examination will be performed, and results collected in the eCRF. The following assessments will be completed as much as possible during each examination: mental status, gait, cerebellar function, cranial nerves, motor function (including strength and reflexes), and sensation. If certain assessments could not be completed due to the subject's inability to cooperate, the reason should be documented.



### 9.1.7 Safety Evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the sponsor or its 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, TEAEs that are serious, considered related to the study treatment or the study procedures, 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.

The following additional clinical safety monitoring and expanded evaluation by the previously established DMC for soticlestat phase 3 clinical studies will utilize the following:

- Electronic data capture (EDC) will have a specific flag that will be checked at enrollment for subjects on concomitant perampanel.
- A daily seizure and medication diary will be used for the study. This will enable review of seizure count data for all subjects.
- The medical monitor and sponsor will closely monitor the seizure frequency counts entered in the daily seizure and medication diary for subjects on concomitant perampanel and will

have a standing agenda item to review data for subjects on perampanel in the medical monitor review meetings.

- Additionally, subjects on perampanel will receive a weekly safety follow-up phone call from site staff during the first 3 months of concomitant use of soticlestat and perampanel.
- If there is a significant increase in seizure frequency rate noted for the subjects on concomitant perampanel, an ad hoc DMC meeting will be called for a review and recommendation by the independent DMC members.
- There will be a standing agenda item for review of seizure frequency rate and safety data for all subjects on concomitant perampanel in the DMC meetings.

#### *9.1.7.1 Ophthalmological Evaluation Procedure*

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

1. Age and developmentally appropriate quantitative visual acuity.
    a) If the subject is unable to perform quantitative visual acuity assessment due to age or developmental ability, a qualitative assessment should be attempted.
2. Bilateral red reflex test (also known as Bruckner transillumination test), to assess for lens abnormalities.
3. Postinstillation of mydriatic eye drop (cyclopentylate is contraindicated in this population with epilepsy), slit lamp (portable acceptable) examination for anterior or posterior lens opacities concerning for cataracts after adequate pupil dilation. For subjects unable to cooperate with slit lamp examination due to age or developmental ability, a 20-D double aspheric binocular indirect ophthalmoscopy lens should be attempted. The use of penlight is acceptable only if the slit lamp and a 20-D double aspheric binocular indirect ophthalmoscope lens evaluations were unsuccessful.
4. Indirect and or direct ophthalmoscopy of the optic nerve and retina after adequate pupillary dilation, preferably with a picture of the fundus.

These evaluations are to be collected annually, at Visit 1, Visit 7 (Week 52), Visit 11 (Week 104), and every 52 weeks afterwards until the study ends, or early termination visit for those subjects who do not complete. The ophthalmological assessments collected at the prospective baseline of the antecedent study will be used as baseline for this study.

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

### *9.1.7.2 ECG Procedure*

For each subject, 12-lead digital ECGs will be collected according to the schedule of study procedures (Appendix A). Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed, when needed to ensure high-quality recordings.

ECGs will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present at the site, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the subject will be assessed by the investigator for symptoms (eg, palpitations, near syncope, syncope) and to determine whether the subject can continue in the study, and the medical monitor or the sponsor should be contacted. The investigator or qualified designee is responsible for determining if any change in subject's management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.



Any clinically significant finding that was not present at baseline will be reported and discussed with the medical monitor or the sponsor. When there are differences in ECG interpretation between the investigator (or qualified designee) and the site/local cardiologist, the investigator (or qualified designee's) interpretation will be used for study entry and immediate subject management. The investigator (or qualified designee) must document his/her review of the ECGs printed at the time of collection.

### *9.1.7.3 Procedures for Clinical Laboratory Samples*

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 details for amounts of blood collected per visit and for the study are provided in Appendix G. The volumes do not exceed 3% of total blood volume over any 4-week period, or 1% of total blood volume at any single time.

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

**Table 9.a Clinical Laboratory Tests**

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| Erythrocytes | Sodium | pH [a] |
| Hemoglobin | Potassium | Protein [a] |
| Hematocrit | Total bilirubin | Glucose [a] |
| | Direct bilirubin | Ketones [a] |
| Red blood cell indices | Indirect bilirubin | Bilirubin [a] |
| Mean corpuscular volume | Alkaline phosphatase | Nitrite [a] |
| Mean corpuscular hemoglobin | Alanine aminotransferase (ALT) | Urobilinogen [a] |
| Mean corpuscular hemoglobin concentration | Aspartate aminotransferase (AST) | |
| Red cell distribution width | Gamma glutamyl transferase (GGT) | Erythrocytes |
| | Blood urea nitrogen (BUN) | Leukocyte esterase |
| White blood cell count and differential | Creatinine | |
| Neutrophils, segmented | Urea | Microscopy |
| Lymphocytes | Calcium | |
| Monocytes | Phosphate | |
| Eosinophils | Glucose | |
| Basophils | Albumin | |
| | Protein | |
| Platelets | Carbon dioxide | |
| Mean platelet volume | Magnesium | |
| | Chloride | |
| | Alpha 1-acidic glycoprotein | |

| Other Serum |
|---|
| Pregnancy test (female subjects only)—choriogonadotropin beta |
| Insulin-like growth factor 1 (IGF-1) (only for subjects who rolled over from TAK-935-3001 or TAK-935-3002 and are aged 2 to 17 years during the study) |

[a] Urinalysis is the primary method. Urine dipstick may be used as a backup only. If sufficient volume of urine cannot be obtained for either central urinalysis testing or dipstick testing in clinic, per investigator's discretion, dipstick tests can be provided to parents/caregivers for home urine testing and results reported to the site for interpretation.



The central laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, and IGF-1. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Local laboratories are allowed after soticlestat dosing for emergent reasons, or when onsite visits turn to virtual visits, or for serum/urine pregnancy tests. The timepoints for collecting samples for hematology, serum chemistries, urinalysis, pregnancy test, and IGF-1 are provided in Appendix A.

It is anticipated that some laboratory values may be outside of the normal value range due to the underlying disease. As in routine practice, the investigators should use their medical judgment when assessing clinical significance. Clinical significance is defined as any variation in laboratory measurements which has medical relevance, and which results in a change in medical care. If clinically significant laboratory changes from baseline are noted, the changes will be documented as TEAEs in the eCRF. The investigator will also assess the relationship to study treatment for all clinically significant out of range values. The investigator will continue to

monitor the subject with additional laboratory assessments until (1) values have reached normal range and/or baseline, or (2) in the judgment of the investigator, out of range values are not related to the administration of study drug or other protocol-specific procedures.

If subjects experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase [GGT], prothrombin time, and international normalized ratio [INR]) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 9.3.1 for the appropriate guidance on reporting abnormal LFTs.)

If ALT or AST remains elevated >3 times the ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as a TEAE (please refer to Section 9.3.1).

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.



### 9.1.8 Documentation of Prior and Concomitant Medications (Including ASM and Rescue)

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

### 9.1.9 Documentation of Concurrent Medical Conditions

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

### 9.1.10 Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed in children aged ≥6 years by use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) [5]. Children who are <6 years old at the start of the study will start this assessment at the next scheduled visit after turning age 6.

The version of the C-SSRS used for all subjects in this study will be the C-SSRS Children's Since-Last-Visit.

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

Suicidal ideation or behavior will be assessed by the use of the C-SSRS. If a subject exhibits signs of suicidal ideation or behavior as per the clinical judgement of the investigator, the subject will be withdrawn from the study as described in Section 7.5. With the identification of positive symptoms of depression and suicidal ideation, the subject will be referred for professional psychiatric assessment and necessary follow-up.

### 9.1.11 Seizure Frequency

Subjects rolling over from TAK-935-3001 were diagnosed with DS; the convulsive seizure types in this study included hemi-clonic or focal clonic, focal to bilateral tonic-clonic, generalized tonic-clonic, bilateral clonic, and convulsive status. Subjects rolling over from TAK-935-3002 were diagnosed with LGS; the MMD seizure types in this study included hemi-clonic or focal clonic, focal to bilateral tonic-clonic, generalized tonic-clonic, bilateral clonic, focal seizures with major motor signs (eg, hypermotor seizures or involving major body areas such as lower extremities or trunk) leading to fall or likely fall, tonic seizures involving major body areas such as lower extremities or trunk leading to fall or likely fall, atonic seizures involving major body areas such as lower extremities or trunk leading to fall or likely fall, and convulsive status.

Seizure frequency will be collected via a paper daily seizure and medication diary. Details will be provided in site documents.

All seizure events will be recorded starting on the day after Visit 1 (Day 1) and until the follow-up visit. At each visit, the paper diary will be reviewed and collected. All entries will be reviewed by the investigator with the subject/parent or caregiver at the time of each visit to ensure proper recording. Any new seizure types that may have occurred since the last visit must be reviewed by the investigator and approved by The Epilepsy Study Consortium (TESC) via submission of a Diary Review Form. Only seizure classification/descriptions approved by TESC will be collected in the daily seizure and medication diary for this study.

### 9.1.12 Health Outcome Measures

For all health outcome variables in this study, baseline refers to the baseline of the antecedent study.

#### *9.1.12.1 CGI-I (Clinician)*

The CGI-I Clinician is a 7-point Likert scale that the investigator uses to rate a subject's improvement in overall seizure control, behavior, safety and tolerability, after the initiation of study drug relative to baseline. The subject will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much

worse), and 7 (very much worse). The investigator or designee will complete the CGI-I at the timepoints specified in Appendix A.

#### *9.1.12.2 Care GI-I (Caregiver)*

The Care GI-I is a 7-point Likert scale that the caregiver uses to rate improvement in overall seizure control, behavior, safety and tolerability after the initiation of study drug relative to baseline. The subject will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The parent/caregiver will complete the Care GI-I via interview at the timepoints specified in Appendix A.

#### *9.1.12.3 CGI-I Seizure Intensity and Duration*

The CGI-I Seizure Intensity and Duration instrument is used by the parent/caregiver to rate changes in intensity and duration of the most impactful seizures from baseline. The subject's symptoms will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The parent/caregiver will complete the CGI-I seizure intensity and duration at the timepoints specified in Appendix A.



#### *9.1.12.4 CGI-I Nonseizure Symptoms*

The CGI-I Nonseizure Symptoms instrument includes 3 single-item assessments that the investigator uses to rate improvement in the caregiver-identified symptoms and impacts in select nonseizure domains (including communication, alertness, and disruptive behaviors) since initiating the study drug. The subject will be rated by the investigator as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse).

The investigator or designee will complete the CGI-I Nonseizure Symptoms instrument in consultation with the primary caregiver at the timepoints specified in Appendix A.

### 9.1.13 Quality of Life Measures

#### *9.1.13.1 Quality of Life Inventory-Disability (Parent/Caregiver Version)*

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

The parent/caregiver-reported questionnaires will be administered according to the schedule of assessments (Appendix A).

*9.1.13.2* CCI [redacted]

[redacted]

*9.1.13.3* CCI [redacted]

[redacted]

*9.1.13.4* CCI [redacted]

[redacted]

### 9.1.14 Optional Blood Sample for Genetic Testing: Potential Exploratory Research

Optional blood samples for genetic testing in LGS subjects will be obtained as indicated in Appendix A. When optional sampling of whole blood for genetic testing occurs, the subject/parent or legal guardian must sign a special informed consent for the genetic testing sample. No sample for genetic testing will be obtained from subjects enrolled in China, France, or Brazil.

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IECs allow, a blood sample will be collected for genetic testing.

The optional blood samples will be coded with the subject number and stored for up to a maximum 15 years after the last subject visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the subject by the investigator or site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

See the laboratory manual for detailed instructions on collecting, handling, storing, and shipping genetic testing samples. Samples will be destroyed according to a process consistent with local regulations. Subjects may request to have their samples destroyed at any time.

### 9.1.15 Optional Caregiver Qualitative Input Substudy

Optional qualitative input data about the subject and caregiver experience in the study will be collected from caregivers according to the schedule of assessments (Appendix A). The qualitative input will be obtained as a substudy of the main study protocol and participating clinical sites will recruit caregivers at the time of enrollment into the main study or at a subsequent study visit. Caregivers must sign a separate ICF to participate. A caregiver's decision not to participate in the substudy will have no effect on the subject's participation in the main study.

Caregiver report of patient experience in clinical studies has been recognized as an important component of patient-focused drug development in rare conditions, particularly when outcome measures used are designed to collect patient-centered outcome measures that involve caregiver input [7]. This optional substudy input will be collected according to the schedule of assessments (Appendix A). The purpose of the substudy is to understand long-term subject and caregiver experience with soticlestat in terms of treatment efficacy, as well as to explore the context and meaning of changes observed during the study. The data collected through the substudy will also be used to support the interpretation of other measures such as CGIs, Care GIs, CGI-I Nonseizure Symptoms, and QI-Disability. Details of the substudy are described in Appendix I.



### 9.1.16 Assessing Palatability and Acceptability

Palatability and acceptability will be assessed in subjects younger than 18 years who take soticlestat tablets or mini-tablets, either intact or crushed and mixed with applesauce, yogurt, or other liquid of similar consistency. Subjects who are administered soticlestat via enteral feeding tubes will not be assessed.

The assessments will be completed by the parents or caregivers on Day 1 and the day after Visit 3 (preferably completed by the same person). For subjects who consent to this amendment after Visit 1, the assessments will be completed on the days after the following 2 scheduled visits (eg, if the subject consents to this amendment at Visit 4, the assessments should be performed on the day after Visit 4 and the day after Visit 5). Parents/caregivers will complete an acceptability/palatability questionnaire within 10 minutes of the morning dose. The questionnaire consists of 6 questions, and uses a 5-point hedonic scale to accommodate subjects with intellectual disability. The parents/caregivers should collect the feedback from subjects and use their own observations to answer the questions. Only in special cases when there is solid

evidence to prove that the subject is capable of understanding the questionnaire and the parent/caregiver is not a suitable assessor (eg, the subject lives independently) will the subject complete the questionnaire by him/herself. It is preferred that the parent/caregiver send a photo or photocopy of the questionnaire to the site right after finishing it. The questionnaire should be brought back to the site during the next visit.

### 9.1.17 Contraception and Pregnancy Avoidance Procedure

#### *9.1.17.1 Male Subjects and Their Female Partners*

Male subjects are not required to use barrier contraception. Donation of sperm is not allowed during the study and within 90 days following the last administration of the study drug.

#### *9.1.17.2 Female Subjects and Their Male Partners*

Serum pregnancy tests will be performed according to the schedule of assessments (Appendix A). For female subjects of childbearing potential, if the investigator judges it necessary, a local laboratory may be used to confirm a negative serum or urine pregnancy test result before the first dose of study drug. Additional pregnancy tests (serum or urine) may be performed by local laboratory throughout the study at the investigator's discretion, and in Years 3 and beyond, pregnancy tests should be done quarterly. A serum or urine pregnancy test will be performed at the subject's last clinic visit.

Please refer to Section 7.1 for inclusion criteria for detailed contraception requirements.

*The following definitions apply for contraception and pregnancy avoidance procedures.*

A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Subjects and parents/legal guardians will be provided with information regarding acceptable methods of contraception as part of the informed consent process and will be asked to sign a consent form stating that there is a clear understanding (including by the parents/legal guardian) of the requirements for avoidance of pregnancy and donation of ova during the course of the study and for 30 days after the last dose of study drug. This consent may be signed by the legally authorized representative of the subject.

During the course of the study, subjects will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures. Pregnancy tests will be administered at Visit 1 and at certain visits following the schedules in Appendix A, and an additional serum or urine human chorionic gonadotropin (hCG) pregnancy test will be performed at the final visit.

*9.1.17.3 General Guidance With Respect to the Avoidance of Pregnancy*

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Assessment of subject compliance through such questions as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late? (Even in women with irregular or infrequent menstrual cycles, a pregnancy test must be performed if the answer is "yes.")
  - Is there a chance you could be pregnant?



### 9.1.18 Pregnancy

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

For female subjects, if the pregnancy occurs during administration of active study drug, eg, after Visit 1 or within 30 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1. For partner of male subjects, if the pregnancy occurs during the study or within 90 days after the last dose, it should be reported following authorization from the subject's partner.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (dose).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

### 9.1.19 Documentation of Study Entrance

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

## 9.2 Monitoring Subject Treatment Compliance

The subject/parent or caregiver will record the study drug taken by subject daily, in the morning and evening.

Confirmation of study drug intake and dosing will be recorded in the daily seizure and medication diary on a daily basis. Any missed doses will be recorded in the daily seizure and medication diary by the subject/parent or caregiver and reviewed by the site personnel. The subject/parent or caregiver will be required to bring used/unused study drug and the daily seizure and medication diary device to each site visit. All subject/parent or caregiver should be re-instructed about the dosing requirements during study contacts. The authorized site personnel conducting the re-education must document the process in the subject's source records.

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

Compliance will be tracked through the subject daily seizure and medication diary and all entries will be reviewed by site personnel, reconciled against returned study drug with queries, as necessary.

Subjects who are significantly noncompliant will be discontinued from the study. A subject will be considered significantly noncompliant if he or she misses more than 20% of study drug during the study duration unless there is a valid reason for interruption in the study drug such as hospitalization. These cases should be discussed with the study monitor. 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.



## 9.3 Safety Monitoring

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

### 9.3.1 Reporting of Abnormal LFTs

If subjects experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.1 for the appropriate guidance on reporting abnormal LFTs.)

If a subject is noted to have elevated ALT or AST >3 times the ULN on 2 consecutive occasions, the abnormality should be recorded as a TEAE or SAE. In addition, eCRFs must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed. The investigator must contact the medical monitor for discussion of the relevant subject details. and possible alternative etiologies. The abnormality should be recorded as a TEAE (please refer to Section 10.2.1).

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, a CRF must be completed and

transmitted with the SAE Report form (as per Section 10.2.2). The investigator must contact the medical monitor for discussion of the relevant subject details, possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions, and continued participation in the study. Follow-up laboratory tests as described in Table 9.a must also be performed.

A consultation with a hepatologist may be considered as per investigator judgement or consultation with the medical monitor or sponsor.

### 9.3.2 Reporting of QTcF Interval Increase

As noted in Section 7.5, if the QTcF is >500 ms or if there is an increase of QTcF >60 msec above baseline, study drug should be discontinued immediately, and the subject should be provided with appropriate clinical follow-up. The subject's ECG findings should be confirmed by repeat ECG with manual measurement of the QTcF interval.

The investigator must contact the medical monitor for discussion of the relevant subject details, possible alternative etiologies, such as medical history/concurrent medical conditions, and continued participation in the study.

In addition, the eCRF must be completed and transmitted with the SAE Report form (as per Section 10.2.2).

If safety monitoring uncovers an issue that needs to be addressed by unblinding the treatment of the antecedent study, only members of the DMC (see Section 11.0) can conduct additional analyses of the safety data.



### 9.3.3 Reporting of Perampanel Drug-Drug Interaction

To assess the potential interaction of soticlestat with perampanel, the following clinical safety monitoring and expanded evaluation will be performed:

- Investigators will perform close monitoring of the seizure frequency counts entered into the daily seizure and medication diary for all subjects, including those on concomitant perampanel.
- Additionally, subjects on perampanel will receive a weekly safety follow-up phone call from site staff during the first 3 months of concomitant use of soticlestat and perampanel.
- The medical monitor and sponsor will provide reviews of the daily seizure and medication diary for subjects on concomitant perampanel including at the regular medical monitoring review meetings. If a significant increase in the blinded review of seizures frequency is detected, an ad hoc DMC meeting will be called for an unblinded review (see Section 11.0).

### 9.3.4 Reporting of Cataracts

To assess the potential for developing cataracts (see Sections 4.3 and 10.1.4), annual ophthalmological evaluations will be performed (see Section 9.1.7.1). If there is a potential finding of cataract, the eCRF must be completed and the abnormality should be recorded as an

AE (or SAE) of special interest following Section 10.2.2. This finding should be promptly communicated to the study team/sponsor.

### 9.3.5 Special Situation Reporting

After transitioning the study to EU CTR, abuse, misuse, medication error, and other uses not foreseen in the protocol must be reported to safety within 7 days of awareness on a paper Special Situation Reporting form.

Definitions:

- Abuse: Persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful physical or psychological effects.
- Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indications(s) or within the legal status of its supply.
- Medication error: An unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor-quality administration) of a medicinal product while in the control of a health care provider, patient, or consumer, which leads to harm or has the potential to lead to harm.

Overdose reporting is described in Section 10.1.2.



## 9.4 Biomarker Samples

Primary specimen collection parameters are provided in Table 9.b.

**Table 9.b Primary Specimen Collection**

| Specimen Name in Schedule of Events | Primary Specimen | Primary Specimen Derivative 1 | Primary Specimen Derivative 2 | Description of Intended Use | Endpoint | Sample Collection |
|---|---|---|---|---|---|---|
| Blood sample for DNA analysis | Blood | DNA | N/A | Pharmacogenetic analysis | Exploratory | Optional [a] |
| Plasma for soticlestat PK | Blood | Plasma | N/A | PK measurements (drug concentrations) | Exploratory | Mandatory [b] |
| Plasma sample for pharmacodynamics | Blood | Plasma | N/A | 24HC analysis | Exploratory | Mandatory [b] |

24HC: 24*S*-hydroxycholesterol; NA: not applicable; PK: pharmacokinetic(s).

[a] Applies only to subjects with Lennox-Gastaut syndrome. Does not apply to subjects enrolled in China, France, or Brazil.

[b] Applies only to subjects from an antecedent study that collected PK and pharmacodynamic samples.

### 9.4.1 Plasma Samples for Soticlestat PK

Blood samples for plasma soticlestat concentration will be collected according to Appendix A. Collection of these samples applies only to subjects from an antecedent study that collected PK and pharmacodynamic samples.

The exact date, time, and dose of last study drug dose before each scheduled visit will be recorded by the subject/parent or caregiver in the daily seizure and medication diary. For subjects who are not able to come for the visit during the morning hours, they should be instructed to take their morning dose, as usual, and come to the study site during the afternoon hours, as feasible for the subject/parent or caregiver. The exact date and time of the PK blood sample collection will be recorded in the eCRF.

Plasma concentrations of soticlestat and its metabolite(s) will be measured by high-performance liquid chromatography with tandem mass spectrometry.

Instructions for collecting, processing, and shipping of plasma samples for soticlestat PK are provided in the laboratory manual.



### 9.4.2 Plasma Samples for Pharmacodynamic Measurements

Blood samples for the measurement of pharmacodynamics to include 24HC levels in plasma will be collected according to the schedule shown in Appendix A. This sample applies only to subjects from an antecedent study that collected PK and PD samples.

Measurements of plasma 24HC levels will be included in this study as a pharmacodynamic biomarker related to the mechanism of action of soticlestat. The conversion of cholesterol to 24HC is a mechanism to maintain cholesterol homeostasis in the brain and its release into the cerebrospinal fluid and plasma [8-10]. Evidence suggests that plasma 24HC levels are mostly derived from the central nervous system [11]. Data from single-rising dose and multiple-rising dose studies showed a decrease in plasma 24HC levels after administration of soticlestat in healthy subjects, which was correlated with the changes in EO percentage measured in the brain using the positron emission tomography radioligand displacement approach (Study TAK-935-1003). In the current study, postdose plasma 24HC levels will be measured to estimate the average EO during a dosing interval in each subject exposed to soticlestat. As no information is available regarding 24HC levels in subjects with epilepsy, baseline data from the antecedent study will be collected for possible future comparisons with aged-matched healthy subjects.

The date, time, and dose of the last dose of the study drug and any ASMs must be captured by the subject/parent or caregiver in the daily seizure and medication diary. The exact date and time of the pharmacodynamic blood sample collection will be recorded in the eCRF.

Instructions for the collection, handling, and shipping of the plasma samples for pharmacodynamics are provided in the laboratory manual.

The actual plasma level as well as change from baseline of the antecedent study in plasma 24HC levels will be summarized. Summary statistics will be reported. Additional pharmacodynamic parameters may be calculated, as appropriate.

### 9.4.3 Blood Sample for DNA Analysis

Sampling of whole blood for genomics (DNA analysis) is optional in this study and will only be performed only for subjects with LGS who provide consent to participate in this assessment. Subjects enrolled in Brazil, China, or France are excluded from participation in this assessment.

There is increasing evidence that an individual's genetic background may impact the PK (absorption, distribution, metabolism, and excretion), pharmacodynamics (pharmacologic effects), and/or clinical effects (efficacy and/or safety) of a drug. DNA research in this study may be conducted to understand how individual genetic variation in subjects impacts their response to study drug treatment.

This information may also be used, for example, to develop a better understanding of the safety, resistance to, and/or efficacy of soticlestat and other study drugs; to increase understanding of the disease/condition being studied and other related conditions; to gain a better understanding of the drug pharmacology; and to generate information needed for research, development, and regulatory approval of tests to predict response to soticlestat.

A whole blood sample for DNA isolation will be collected from each participant who provides informed consent. Because genetic analysis is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Subjects who consent and provide a blood sample for DNA analysis can withdraw their consent at any time and request disposal of a stored sample. Any remaining sample that can be identified as coming from the subject will be destroyed. The investigator and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

Detailed instructions for the collection, handling, and shipping of blood for DNA samples are provided in the laboratory manual.



## 9.5 Biological Sample Retention and Destruction

If permitted by local regulations and with written consent of the subject/parent or legal guardian, the sponsor will store blood left from clinical laboratory tests for potential future research related to soticlestat and/or seizure disorders. The samples will be held for up to 15 years after the end of the study. The samples will be stored securely at sample storage facilities at the expense of the sponsor and only be identified by a unique code such that no one will be able to link the sample to a subject.

Subjects who consented to stored samples for future research can withdraw their consent and request disposal of a stored sample at any time. The site will notify sponsor of consent withdrawal. If samples have been analyzed, results may not be able to be removed from the study.

Detailed instructions for biological sample retention and destruction are provided in the ICF.

### 9.6 Schedule of Study Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit(s)/time point(s).

#### 9.6.1 Unscheduled Visits

Subjects may return to the study center for unscheduled visits as needed. Unscheduled study visits can be performed when the subject has a study-related issue in between regular study visits per investigator discretion.

The following should be performed during this visit:

- Documentation of concomitant medications.
- TEAE assessment.
- Other procedures, including dose adjustments, as deemed appropriate by the investigator.
- These visits can also be performed as virtual visits or home visits by the site staff, depending on the planned assessments and per the investigator's judgment (as allowed by local regulations).

#### 9.6.2 Poststudy Care

Study drug may be available upon completion of the subject's participation in the study, as this study is anticipated to continue until soticlestat is approved and launched. The subject should be returned to the care of a physician and standard therapies initiated or resumed as required.



## 10.0 COLLECTION AND REPORTING OF ADVERSE EVENTS

### 10.1 Definitions

In this study, AE refers to both pretreatment events (PTEs) and TEAEs. PTEs are defined as AEs that start after the signing of informed consent but before receiving any study drug in this study. TEAEs are defined as AEs that start after the first dose of open-label study drug in this study. Any PTEs (for the current study) that are attributed to the antecedent studies will be collected under the antecedent study.

#### 10.1.1 AEs

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

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

### 10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately AEs.

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required, or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased serum creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or a TEAE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the event term recorded captures the change in the condition from baseline (eg "worsening of…").

- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as a TEAE. Investigators should ensure that the event term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at doses above that is assigned to that individual subject according to the study protocol. Cases of overdose with any medication without manifested side effects are NOT considered AEs but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF. A report of overdose in the eCRF will trigger a reporting of the event within 7 days of awareness.

### 10.1.3 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.



### 10.1.4 AEs of Special Interest

An AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

- Potential drug-drug interaction between soticlestat and perampanel leading to increased seizure frequency:

  A potential drug-drug interaction with perampanel and soticlestat resulting in increased seizure frequency was noted in 3 subjects in the TAK-935-2001 study of adult subjects with DEEs. To assess this potential interaction, clinical safety monitoring and expanded evaluation will be performed to closely monitor seizure frequency in these subjects (please see Section 9.3.3).

- Cataracts:

  During nonclinical studies, incipient posterior cortical, subcapsular lenticular cataracts of moderate grade were seen in 1 male rat at 300 mg/kg/d and in 1 female rat at 100 mg/kg/d. To assess these potential changes, a detailed ophthalmological monitoring and evaluation will be performed. (Please see Section 9.1.7.1 and Section 9.3.4.)

- Psychosis:

  During the phase 1 multiple rising dose study in healthy subjects, episodes of confusion, euphoria, and psychosis were seen at the highest dose of 600 mg/day. However, in this study subjects were not up-titrated to the target dose. Psychiatric AEs should be monitored closely by the investigator and reported based on AE/SAE criteria described in Section 10.1.3.

AEs of special interest must be recorded as AEs of special interest in the AE eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor if requested.

### 10.1.5 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

| | |
|---|---|
| Mild: | The event is transient and easily tolerated by the subject. |
| Moderate: | The event causes the subject discomfort and interrupts the subject's usual activities. |
| Severe: | The event causes considerable interference with the subject's usual activities. |

### 10.1.6 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

| | |
|---|---|
| Related: | An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible. |
| Not Related: | An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments. |



### 10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

### 10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

### 10.1.9 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

### 10.1.10 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

### 10.1.11 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE (eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE).
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Dose interrupted – the dose was interrupted due to the particular AE.



### 10.1.12 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or sign/symptom has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, sign/symptom, or laboratory value on the last day of the observed study period is worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "not recovered/not resolved."
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AE is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

## 10.2 Procedures

### 10.2.1 Collection and Reporting of AEs

#### *10.2.1.1 AE Collection Period*

Collection of TEAEs will commence from the first dose of study drug on Day 1. Routine collection of TEAEs will continue until the follow up visit.

#### *10.2.1.2 AE Reporting*

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing TEAEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until a satisfactory explanation for the changes is observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

Subject diary and/or health outcome/quality of life measures will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up, if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

### 10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

- Regardless of causality, SAEs must be reported to the sponsor Global Pharmacovigilance department or designee, to the attention of the individual identified in the information list, which will be provided in the study manual, within 24 hours of becoming aware of the event. This will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible within 24 hours, then a paper-based SAE form must be completed and transmitted as facsimile. If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

## 10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.



### 10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the EMA, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC.

# 11.0 STUDY-SPECIFIC COMMITTEES

Details of the DMC are captured in a DMC charter written before the start of the study.

## 12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

### 12.1 Source Documents

All key data must be recorded in the subject's source documents unless otherwise noted in the protocol. Source documents may be paper or electronic, including data obtained using electronic devices and associated technologies. Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, appointment books, diaries, COAs, original clinical laboratory reports, histology reports, pathology reports, brain imaging, and electroencephalogram. The investigator (as listed on the US Food and Drug Administration [FDA] Form 1572) is responsible for maintaining adequate and accurate source documents.

### 12.2 eCRFs

Completed eCRFs are required for each subject who signs an informed consent form. The eCRFs are designed to record all observations and other data pertinent to the clinical investigation unless otherwise noted in the protocol.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. eCRFs must be completed in English.

The investigator or the investigator's designee (ie, authorized site personnel, as stated in the site delegation log) must enter data from the source documents (Section 12.1) into the eCRF with guidance from the study CRF Completion Guidelines.

No data will be entered directly into the eCRFs as source data. The site is required to have separate source documentation and transcribe the data into the eCRF.

The following data will not be recorded into the eCRFs:

- IRT data.
- Central laboratory data.
- PK data.
- Pharmacodynamic data.
- Caregiver substudy data.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After submission of the CRFs to the sponsor, any change of, modification of or addition to the data on eCRFs should be made by the investigator with use of change and modification records of eCRFs (data clarification form) provided by the sponsor. The principal investigator must review the data clarification form for completeness and accuracy, and must sign and date the form.

After the lock of the study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with the approval from the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.



## 12.3 Record Retention

The following procedure is applicable for all countries except Japan.

The investigator agrees to keep the records stipulated in Section 12.2 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), including consent to use digital tools and applications, if applicable, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The following procedure is applicable for Japanese sites only.

The investigator and the head of the study site agree to keep the records stipulated in Section 12.2 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the study site to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and/or the head of the study site and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.



# 13.0 STATISTICAL METHODS

## 13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before subjects are enrolled in this open-label study. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

## 13.2 Determination of Sample Size

The sample size is determined by the number of subjects who roll over from the antecedent studies (approximately 150 subjects with DS and 250 subjects with LGS; approximately 400 total subjects). No formal power/sample size calculation is performed.

### 13.2.1 Analysis Sets

#### *13.2.1.1 Safety Analysis Set*

All treated subjects (subjects who take at least 1 dose of study drug) will be included in the safety analysis set. Safety analyses will be based on indication (DS or LGS).

#### *13.2.1.2 Intent-to-Treat Analysis Set*

All enrolled subjects will be included in the intent-to-treat (ITT) analysis set. All ITT analyses will be based on indication (DS or LGS).

#### *13.2.1.3 Modified Intent-to-Treat Analysis Set*

All enrolled subjects who have received at least 1 dose of study drug and have been assessed for seizures for at least 1 day in the treatment period will be included in the modified ITT (mITT) analysis set. All mITT analyses will be based on indication (DS or LGS)

### 13.2.2 Analysis of Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed for enrolled subjects by indication (DS or LGS) and overall. Descriptive statistics will be used to summarize data for continuous variables such as age and weight (eg, number of subjects, mean, median, SD, and range) and for such categorical variables as sex, ethnicity, and race (number and percentage of subjects within each category). Medical history and medication history will be listed by subject.



### 13.2.3 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.

### 13.2.4 Safety Analysis

Descriptive statistics will be used to summarize all safety endpoints by indication (DS or LGS). All AEs will be coded using MedDRA. AEs will be summarized using Preferred Terms and primary System Organ Classes.

Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight, and ECG parameters, as appropriate.

Details will be provided in the SAP for appropriate summaries based on data type for these assessments.

Baseline for safety analysis (eg, vital sign) is the baseline of the antecedent study unless indicated otherwise.

### 13.2.5 Efficacy Analysis

Efficacy analyses will be performed on the mITT analysis set. The seizure frequency will be calculated for each indication (DS or LGS) based on all data collected during the treatment period. The seizure frequency endpoints will be summarized by indication (DS or LGS) for every 12-week period starting from date of first dose of the study. Distribution-free 2-sided 95% CIs for the median will be provided.

CGI-I, Care GI-I, CGI-I Seizure Intensity and Duration, CGI-I Nonseizure Symptoms, and QI-Disability score will be summarized descriptively for each visit where they were collected and at end of study. The count and percentage of each category/question will be provided by visit. Global impression of improvement scales (CGI-I, Care GI-I, CGI-I Seizure Intensity and Duration, and CGI-I Nonseizure Symptoms) will also be summarized dichotomously in terms of the number and proportion of participants who gave responses of minimally improved or better. Two-sided 95% CIs will be presented for proportions for dichotomous categories. Details will be provided in the SAP for appropriate summaries based on data type for these assessments.

Baseline for efficacy analysis is the baseline of the antecedent study unless indicated otherwise.

### 13.2.6 Exploratory/Additional Analyses

CCI [redacted] the number of days that rescue ASM is issued, CCI [redacted] will be analyzed descriptively. Appropriate descriptive and graphical analyses will be used to summarize results from the exploratory endpoints. Data from the caregiver qualitative input study will be analyzed and reported independently of the main study data.

The proportion of days when rescue ASM is used during the study period will be summarized descriptively.

The caregiver's and subject's experience (performed in selected sites) will be listed.

CCI [redacted].

Alpha 1-acidic glycoprotein will be analyzed as part of the laboratory serum chemistry panel at each visit where PK samples are obtained.

Plasma concentrations of soticlestat and its metabolite(s) will be summarized and displayed graphically per nominal time points. Mean plasma concentrations over time will be presented graphically.

Correlation of change in soticlestat exposure (PK) or plasma 24HC (pharmacodynamics) with efficacy (change in seizures over the full treatment period) will be investigated.

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

Details will be provided in the SAP for appropriate summaries based on data type for these assessments.

Baseline for exploratory analysis is the baseline of the antecedent study unless indicated otherwise.

## 13.3 Other Statistical Issues

### 13.3.1 Missing or Invalid Data

The analysis will be based on as-observed data. No imputation will be implemented.

Any deviation from the final statistical analysis plan will be documented in the clinical study report.

### 13.3.2 Interim Analyses

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

# 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. Monitoring visits can be virtual or on site, as indicated in the clinical monitoring plan. The investigator guarantees access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

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

If rSDV 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.

## 14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A protocol deviation form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The sponsor will assess any protocol deviation. If it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The following procedure applies to Japanese sites only:

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

## 14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan, Center for Drug Evaluation [CDE] in China). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site (or in Japan, the head of the study site) guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

## 15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix D. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

### 15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the US Department of Health and Human Services (for studies including TDC Americas).

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study.



Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

## 15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies (if applicable). The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.



If the subject is not capable of rendering adequate written informed consent (including minors or adults with intellectual disability), then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations. Minors or adults with intellectual disability comprise most of the patients with LGS or DS, therefore, the study would not be representative of these patient populations if it excluded them.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ballpoint ink in the case of written consent. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent or after the receipt of subject signature (in the

case of consent) and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable.

Once signed, the original informed consent form or certified copy (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) will be maintained by the study site. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be provided to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

A separate informed consent form for the optional caregiver qualitative input substudy (see Section 9.1.15) must be signed by the caregiver.



## 15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials, may be used to verify the subject and accuracy of the subject's unique identification number.

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 9.1.1).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

## 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

### 15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.



### 15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

## 15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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# Appendix A Schedule of Study Procedures

## Part 1: Main Schedule

| Assessment | Base-line [a] | Year 1 | | | | | | Year 2 | | | | Year 3 | | Year 4+ | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | | **1** | **1** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **30** | **36** | **Every 6 Months** | **Every 12 Months** | **EOM [b] +1** |
| **Study Week (Last Day)** | **-1 (Day -1)** | **1 (Day 7) [c]** | **4 (Day 28)** | **13** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **130** | **156** | **Every 26 Weeks** | **Every 52 Weeks** | **EOM+3 (EOM +21 days)** |
| **Visit Windows (Days)** | | **±3** | **±7** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±30** | **±30** | **±30** | **±30** | **+7** |
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **Unnum-bered and EOM [b]** | **Unnum-bered and EOM [b]** | **Not applicable** |
| Informed Consent/Assent | X | | | | | | | | | | | | | | | |
| Inclusion/ Exclusion | X | | | | | | | | | | | | | | | |
| Medical history | X [d] | | | | | | | | | | | | | | | |
| Concomitant medications | X | X [c] | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Adverse events [d] | X [e] | X [c] | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Height | X | | | | | | X | | X | | X | | X | X | | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| 12-lead ECG [f] | X | | | X | X | | X | | X | | X | X | X | X | | |
| Physical examination [g] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Neurological examination | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Ophthalmologic-al examination | X | | | | | | X | | | | X | | X | | X | |

| Assessment | Base-line [a] | Year 1 | | | | | | Year 2 | | | | Year 3 | | Year 4+ | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | | **1** | **1** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **30** | **36** | **Every 6 Months** | **Every 12 Months** | **EOM [b] +1** |
| **Study Week (Last Day)** | **-1 (Day -1)** | **1 (Day 7) [c]** | **4 (Day 28)** | **13** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **130** | **156** | **Every 26 Weeks** | **Every 52 Weeks** | **EOM+3 (EOM +21 days)** |
| **Visit Windows (Days)** | | **±3** | **±7** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±30** | **±30** | **±30** | **±30** | **+7** |
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **Unnum-bered and EOM [b]** | **Unnum-bered and EOM [b]** | **Not applicable** |
| Serum/urine pregnancy test [h] | X | | | X | X | | X | | X | | X | | X | X | | |
| Blood samples for hematology and serum chemistry; urine samples for urinalysis | X | | | X | X | | X | | X | | X | | X | | X | |
| Blood sample for IGF-1 [i] | X | | | | | | X | | | | X | | X | | X | |
| Plasma sample for soticlestat PK [j] | X | | | X | X | | X | | X | | X | | X | | X | |
| Plasma sample for pharmaco-dynamics [j] | X | | | | X | | X | | X | | X | | X | | X | |
| Blood sample for DNA analysis [k] | | | | X | | | | | | | | | | | | |
| Contact IRT for subject ID/ medication ID/ subject status | X | X [c] | X | X | X | X | X | X | X | X | X | X | X | X | | |

| Assessment | Base-line [a] | Year 1 | | | | | | Year 2 | | | | Year 3 | | Year 4+ | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | | **1** | **1** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **30** | **36** | **Every 6 Months** | **Every 12 Months** | **EOM [b] +1** |
| **Study Week (Last Day)** | **-1 (Day -1)** | **1 (Day 7) [c]** | **4 (Day 28)** | **13** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **130** | **156** | **Every 26 Weeks** | **Every 52 Weeks** | **EOM+3 (EOM +21 days)** |
| **Visit Windows (Days)** | | **±3** | **±7** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±30** | **±30** | **±30** | **±30** | **+7** |
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **Unnum-bered and EOM [b]** | **Unnum-bered and EOM [b]** | **Not applicable** |
| Dispense study drug and provide medication and seizure diary [c] | X [c] | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Study drug return for compliance/ accountability [c] | | | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Collect medication and seizure diary [c] | | | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| C-SSRS | X | | | X | X | | X | | X | | X | X | X | X | | |
| CGI-I (Clinician) | X [e] | | | X | X | X | X | X | X | X | X | X | X | X | | |
| Care GI-I | X [e] | | | X | X | X | X | X | X | X | X | X | X | X | | |
| CGI-I Seizure Intensity and Duration | X [e] | | | X | X | X | X | X | X | X | X | X | X | X | | |
| CGI-I Nonseizure Symptoms | X [e] | | | X | X | X | X | X | X | X | X | X | X | X | | |
| CCI | | | | | | | | | | | | | | | | |
| QI-Disability | X [e] | | | | X | | X | | X | | X | X | X | X | | |

| Assessment | Base-line [a] | Year 1 | | | | | | Year 2 | | | | Year 3 | | Year 4+ | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | | **1** | **1** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **30** | **36** | **Every 6 Months** | **Every 12 Months** | **EOM [b] +1** |
| **Study Week (Last Day)** | **-1 (Day -1)** | **1 (Day 7) [c]** | **4 (Day 28)** | **13** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **130** | **156** | **Every 26 Weeks** | **Every 52 Weeks** | **EOM+3 (EOM +21 days)** |
| **Visit Windows (Days)** | | **±3** | **±7** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±30** | **±30** | **±30** | **±30** | **+7** |
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **Unnum-bered and EOM [b]** | **Unnum-bered and EOM [b]** | **Not applicable** |
| CCI | | | | | | | | | | | | | | | | |
| Dispense acceptability/ palatability questionnaire [l] | X | | X | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | |
| Selected sites only: Caregiver qualitative input substudy | | | | | | | X | | | | X | | X | | X | |

Abbreviations: 24HC, 24*S*-hydroxycholesterol; AE: adverse event; Care GI-I, Caregiver Global Impression of Improvement; CCI [redacted]; CGI-I, Clinical Global Impression of Improvement; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; eCRF, electronic case report form; EOM, end of Maintenance Period; CCI [redacted]; ET, early termination; ID, identification number; IGF-1, insulin-like growth factor 1; IRT, interactive response technology; LGS, Lennox-Gastaut syndrome; PD, pharmacodynamic(s), PK, pharmacokinetic(s); QI-Disability, Quality of Life Inventory-Disability.

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, all visits except Visit 1 could be turned into virtual visits (or home visits in jurisdictions where allowed) to monitor subject safety. In such cases, the following study procedures should be completed in local clinics whenever possible: clinical laboratory tests, serum or urine pregnancy test, growth-related hormones, vital signs, height, weight, physical examination, neurological examination, ophthalmological examination, and ECG.

[a] The end of treatment visit in the prior study can be combined with Visit 1 in this study. If these 2 visits are on different days, collection of concomitant medication, serum pregnancy test, C-SSRS, and ECG should be repeated on Visit 1. Other identical safety assessments (weight, height, vital signs, physical examination, neurological examination, ophthalmological examination, hematology and serum chemistry, urinalysis) taken at the subject's last visit of the prior study do not need to be repeated if they're performed within 21 days before Visit 1, but could be performed at the discretion of the investigator.

Subjects rolling-over from prior open-label phase 3 studies can directly start from the maintenance period, and the treatment period in the antecedent study will be counted into the maintenance period of this study (for example, if the treatment period in the antecedent study is 1 year, the subjects will start from Year 2 after rolling over to this study, meaning that the subjects will have Visit 1, and after 13 weeks Visit 9 will be conducted.

[b] The subject's last visit on the maintenance dose (EOM) will be the scheduled or ET visit at which it is determined the subject should be discontinued from the study. At this time, the subject will begin an approximately 1-week period of dose tapering (as determined by the investigator for the ET subjects) 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 ET visit, have visit assessments performed, be started on dose tapering, and have a follow-up visit or phone call scheduled.

[c] After the first dose on Day 1, a safety follow-up call will be made. Visit 2 (Day 7) can be at the study site or, at the discretion of the subject/parent or caregiver and the investigator, substituted with a phone call. The study drug and the medication and seizure diary dispensed at Visit 1 (Day -1) will be sufficient to cover subjects who do not come to the site at Visit 2, and will be returned at Visit 3 (Day 28). Note: Subjects on perampanel will receive a weekly safety follow-up phone call from site staff during the first 3 months of concomitant use of soticlestat and perampanel.

[d] For subjects with ongoing AEs in the prior study, their ongoing AEs at the time of consent should be recorded as medical history in this open-label extension study.

[e] Data for CGI-I (Clinician), Care GI-I, CGI-I Seizure Intensity and Duration, CGI-I Nonseizure Symptoms, QI-Disability, CCI from the end of treatment visit of the antecedent study may be carried over and recorded in the eCRF in this study if these data are available and collected within 21 days before Visit 1.

[f] 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.

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

[h] For female subjects of childbearing potential, if the investigator judges it necessary, a local laboratory may be used to confirm negative serum or urine pregnancy test result before the first dose of study drug. Apart from the scheduled serum pregnancy tests shown here, additional pregnancy tests (urine only) may be performed throughout the study at the investigator's discretion. A serum or urine pregnancy test will be performed at the patient's last clinic visit.

[i] Only collected for subjects who rolled over from antecedent studies TAK-935-3001 or TAK-935-3002, and are 2 to 17 years old during this study.

[j] PK and pharmacodynamic samples will be collected only from subjects who provided these samples in the antecedent study.

[k] Optional collection. Applies only to subjects with LGS. Does not apply for subjects enrolled in China, France, or Brazil.

[l] For subjects younger than 18 years only. The assessments will be completed by the parents or caregivers on Day 1 and the day after Visit 3. For subjects who consented to this amendment (2) after Visit 1, the assessments will be completed on the days after the following 2 scheduled visits (eg, if the subject consented to this amendment (2) on Visit 4, the assessments should be performed on the day after Visit 4 and the day after Visit 5).

## Part 2: Schedule of Mandatory Safety Phone Calls

| Day | Phone Call | Purpose of Follow-up Phone Call | Scheduled Dose Level |
|---|---|---|---|
| Day 2 or Day 3 | 1st call | Safety and tolerability | Dose 2 |
| Day 7 | 2nd call | Up-titration (Dose 2 to Dose 3) or taper (Dose 2 to Dose 1) | Dose 2 |
| Day 8 or Day 9 | 3rd call | Safety and tolerability (taper allowed) | Dose 3 |
| Day 14 | 4th call | To end titration period | Dose 3 |

Subjects on concomitant perampanel will also receive weekly safety calls during the first 3 months.

## Appendix B Strong CYP3A Inducers

Strong inducers of CYP3A are prohibited, except antiseizure medication. Examples of prohibited inducers are listed below. (Source: fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers, Table 3-3 [inducers], accessed 06 March 2022.)

| **Strong CYP3A Inducers (examples)** |
|---|
| Apalutamide |
| Enzalutamide |
| Mitotane |
| Rifampin |
| St. John's wort |

## Appendix C Virtual Visits and Trial Management During COVID-19 Pandemic and Other Extenuating Circumstances

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, or other extenuating circumstances, such as war or natural disaster. This section addresses situations in which scheduled in-person clinic visits are not feasible due to local, regional, or national restrictions.

COVID-19 vaccination of subjects is allowed during the study.

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 trial due to the ongoing COVID-19 pandemic.

Due to the COVID-19 pandemic or other extenuating circumstances, such as war or natural disaster, 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 trials during the pandemic.

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 in order to monitor subject safety.

Virtual visits, if aligned with institutional or local guidelines, to ensure a point of contact between subjects/parents/caregivers and site staff, can be conducted via phone or via any platforms approved by local regulations. This flexibility of communication is not expected to negatively affect subject safety or study data integrity.

A decentralized clinical trial platform may be used to conduct the virtual visits, if permitted by local regulations. The site will ensure that any related subject data privacy aspects are appropriately managed and will obtain subjects' consent for the use of the platform for virtual visits.

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, if in alignment with institutional or local guidelines and as allowed by local regulations. A process has been put in place to ensure shipment traceability, proper temperature control conditions, study drug 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, rSDV may be considered for critical data related to subject's safety and any key variables to ensure data accuracy / integrity.

If rSDV 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 (nonroutine/nonstandard 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 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 a 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 Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the

subject's legally acceptable representative (parent or legal guardian) may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative (parent or legal guardian) will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use effective (not applicable for Germany) or highly effective contraception (as defined in the informed consent) from the time of signing informed consent throughout the duration of the study, and for 30 days following the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued.
26. Male partners of female subjects must use effective (not applicable for Germany) or highly effective contraception (as defined in the informed consent) if required as part of the method (eg, double-barrier, vasectomized partner) from signing the informed consent throughout the duration of the study, and for a minimum of 30 days following the last dose of study drug.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

## Appendix F Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

## Appendix G Blood Volumes

The amount of blood collected from subjects at any single visit and at all scheduled visits during the study will be the volumes as shown in the table for the respective weight categories. Additional blood may be drawn for retests or unscheduled visits, if any, and will not exceed the volume indicated for each weight group.

**Blood Sample Volumes (mL) by Visit and Subject Weight**

| Subject Weight | Base-line V1 [a] | V4 | V5 | V7 | V9 | V11 | V13 | EOM /ET | Unsched-uled/ Retest [b] | Total, Scheduled Visits |
|---|---|---|---|---|---|---|---|---|---|---|
| 10-15 kg | 7.9 | 5.5 | 7.5 | 7.9 | 7.5 | 7.9 | 7.9 | 7.9 | 7.9 | 60.0 |
| >15-45 kg | 11.6 | 8.1 | 11.1 | 11.6 | 11.1 | 11.6 | 11.6 | 11.1 | 11.6 | 87.8 |
| >45 kg | 13 | 9.5 | 12.5 | 14.0 | 12.5 | 14.0 | 14.0 | 12.5 | 13.0 | 102.0 |

See the laboratory manual for details.

ET: early termination.

[a] Blood volumes may vary slightly if performed by a local laboratory or by central antiseizure medication testing laboratory in China.

[b] Unscheduled retests are allowed at investigator discretion. Scheduled and unscheduled blood sample volumes must not exceed 3% of total blood volume over any 4-week period, or 1% of total blood volume at any single time.

Sites will be advised not to attempt collection of blood if they fail twice. Another attempt can be made after 2-4 weeks.

Weight is measured to 1 decimal place for determining dosing bands. Thus, 44.9 kg would be in the 30 to <45 mg band.



These volumes represent the approximate maximum for visit and weight.

## Appendix H Minimizing Stress and Pain for Study Subjects

To follow the EU expert group recommendations on *Ethical considerations for clinical trials on medicinal products conducted with minors* (revision 1 dated 18 September 2017), the following measures have been implemented to reduce stress and pain for the study subjects:

For participating subjects including pediatric subjects, the risk associated with the administration of soticlestat is low, as it was generally safe and well tolerated in phase 1 and phase 2 studies. The risk associated with the diseases under study is mitigated by allowing concomitant antiseizure therapies (including ASMs, ketogenic diet, VNS, surgery, etc) to be adjusted and rescue ASMs to be used during the study. Regular as well as ad hoc DMC meetings have been held to monitor the safety of the study participants.

Study procedures have been streamlined to reduce the risks and burdens to the study participants. Most study procedures are usually conducted during an SOC epilepsy clinic visit and induce little risk or burden (eg, vital signs, physical examination, neurological examination, clinical laboratory tests, ECG). Procedures that are not included in SOC clinic visit, including ophthalmological examination with pupil dilation, C-SSRS, PK and PD sampling, and optional genetic testing, do not have significant risks or burdens and are designed to collect critical information on AEs of special interest, class effect of ASMs, or to provide crucial scientific data. Topical anesthetic cream can be applied before taking blood samples. The needles used for blood sampling are butterfly needles, which are less painful to use and easier to access veins that are small or narrow. Butterfly needles with smaller size (23 gauge) are used in subjects weighing ≤45 kg, while 21 gauge are used in subjects weighing >45 kg. Sites will be advised not to attempt collection of blood if they fail twice. Another attempt can be made after 2-4 weeks. Blood volume collected has been minimized based on weight in children, as specified in Appendix G.



Study visits and procedures have also been designed to minimize the burdens to the parents/caregivers. Study visits are infrequent to reduce the burden of traveling to sites (about 3 months apart before Year 3, and 6 months apart starting from Year 3). In addition, in jurisdictions where home visits by site staff in clinical studies are allowed, these may be used as an alternative to site visits to further alleviate the parents'/caregivers' burden. Virtual visits are also allowed in case of COVID-19 travel restrictions or other extenuating circumstances, and study procedures related to safety examinations are allowed to be performed locally. Parents/caregivers need to complete a set of health outcome measures during certain visits and keep a seizure and medication diary. The number and complexity of these measures as well as the content of the diary have been minimized to reduce their burden.

In summary, the risks and burdens are low and acceptable in this study. To the study participants and their parents/caregivers, the elements of the study are unlikely to cause significant pain, discomfort, fear, disturbances of their lives and personal activities, or otherwise unpleasant experiences.

## Appendix I Substudy Synopsis/Procedures

| **Full title** | **A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies to Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects With Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2): Caregiver Qualitative Input Sub-Study** |
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| Study background | Takeda has developed a new medication, soticlestat, to treat seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS). These syndromes are characterized by multiple types of medically refractory seizures that contribute to severe cognitive and neurologic delays and declines, as well as a range of social, behavioral, and communication problems.<br><br>Clinical Outcomes Solutions (COS) has been working closely with Takeda on the development of a clinical outcomes assessment (COA) strategy for the soticlestat trial program and has collaborated with Takeda scientists to develop a new clinician-reported measure: the Clinical Global Impression of Improvement (CGI-I) Nonseizure Symptoms. Additionally, COS has conducted qualitative interviews with caregivers of those with LGS and DS to learn about the caregiver perspective and debrief both the CGI-I Nonseizure Symptoms and the Quality of Life Inventory – Disability (a quality of life measure for use in children and adolescents with intellectual disabilities).<br><br>Takeda has requested that COS assist Takeda with further exploring the caregiver and patient experience in LGS and DS. Following the Phase 3 trials (TAK-935-3001 and TAK-935-3002), Takeda plans to enroll patients and their caregivers into a ~ 4-year open-label extension (OLE, TAK-935-3003) study, *A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies to Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects with Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2) Open-Label Extension Study of Soticlestat in Dravet and Lennox-Gastaut Syndromes*. To fully explore the long-term outcomes of treatment with soticlestat, COS proposes to conduct a longitudinal qualitative sub-study with caregivers enrolled in ENDYMION 2 at Year 1. Interviews are also planned for subsequent years of the trial (as per the schedule of assessments), eg, end of Year 2, 3, and 4, to continue to explore long-term outcomes of treatment with soticlestat. |
| Study objectives | The aim of this project is to conduct a qualitative sub-study with caregivers enrolled in ENDYMION 2 at time points specified in the schedule of assessments (Appendix A), in order to explore long-term outcomes associated with treatment with soticlestat. Specific aims are:<br><br>• To further explore the CGI-I Nonseizure Symptoms (a clinician reported outcome [ClinRO]) with caregivers of patients with LGS |

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| | or DS, to obtain caregiver views on changes across the 3 nonseizure concepts.<br>• To gain qualitative insights into any improvements in patient's seizure and non-seizure symptoms, and the impacts associated as well as insights into the experience of the caregiver (eg, general health, quality of life, social/emotional well-being, work) and impact on family.<br>• To gain qualitative insights around treatment satisfaction, administration, and overall trial experience.<br>This information can aid in collecting data on outcomes that have not been explored in the pivotal trials or other key studies and can help gain additional understanding on benefits identified in prior studies. |
| Study design | N = 75 semi-structured qualitative interviews will be conducted remotely (via telephone or online videoconferencing system) with caregivers of patients with LGS and DS who are enrolled in Takeda's ENDYMION 2 clinical trial. Each interview is expected to last approximately 60 minutes.<br>The proposed qualitative interviews will be conducted as a sub-study aligned to ENDYMION 2 and will be conducted under the ethics approval for the trial. This sub-study is optional, and caregivers will be consented into the sub-study by the relevant site.<br>Caregivers will be recruited from 5 different countries (United States, Netherlands, Poland, Spain, and China), with interviews taking place according to the schedule of assessments (Appendix A). For subsequent years, the mix of countries may change.<br>The intention is to recruit approximately n = 28 caregivers from the US, n = 18 from China, n = 10 from the Netherlands, n = 10 from Poland, and n = 9 from Spain. It is intended that the proportion of caregivers will be approximately 60-70% caregivers of those with LGS, and 30-40% caregivers of those with DS, in line with expected recruitment proportions for ENDYMION 2.<br>While efforts will be made to ensure that these targets are met, the final study sample and sites will be based upon those available for recruitment and willing to participate. Therefore, these are used as targets for recruitment rather than requirements. |
| Participant selection criteria | Patients and their caregivers would have been screened for eligibility within enrolment into the clinical trial. No additional inclusion/exclusion is required, other than:<br>Must have completed the Week 52 visit of the OLE;<br>Have consented to take part in the patient experience interview;<br>Be willing/able to participate in a telephone or web assisted video |

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| | interview within the appropriate time window;<br>Be fluent in the language required for interview being conducted. |
| Recruitment procedures | Site training will be provided to activated sites that have agreed to be involved in the sub-study. This training will provide a rationale of the study and an overview of key responsibilities.<br>Since the interview sub-study will occur alongside ENDYMION 2, the clinical trial clinic visits will be utilized to remind the clinical trial subjects of the potential for sub-study involvement. The aim will be to consent caregivers on or before the Week 39 visit. Whereby subjects have entered the OLE at an earlier point, some may be consented at the Week 52 visit. Where possible, caregivers will be interviewed within a 4-week window of the relevant visit indicated on the schedule of assessments (Appendix A). The decision to interview any caregiver beyond the 4-week time window, if needed, will be confirmed, and agreed upon with Takeda on a case-by-case basis prior to scheduling the interview.<br>Sites will obtain consent for the sub-study. For those caregivers willing to take part in the interview, sites will need to fill out a caregiver contact form that records the caregiver's name, telephone number, email address, the subject's unique ENDYMION 2 identification number, basic caregiver demographic information, as well as the projected date for the next study visit related to the caregiver qualitative input sub-study. This information will be sent securely to COS to allow for initial contact and scheduling of interviews. This will be sent via a secure HIPAA and General Data Protection Regulation (GDPR)-compliant file sharing site, Dropbox Pro and the link for this will be provided in the caregiver contact form,<br>Once CRO have provided a list of key contacts for each of the sites, COS can then directly communicate with key site personnel. CRO will be the point of contact if a site becomes unresponsive or if issues arise that cannot be resolved between the site and COS. CRO may also be used as the point of contact whereby there are translation issues between sites and COS.<br>COS will reach out to sites 2 weeks prior to the subject's intended caregiver qualitative input sub-study visit to confirm this is still scheduled. After the relevant study visit has passed, COS will confirm with the site that the visit occurred and will then contact the caregiver to schedule an interview. Interviews will be scheduled at a time convenient for caregivers, and within approximately 4 weeks of the study visit, where possible to do so. The caregiver will be asked to identify a time that they can participate in the interview in a private, quiet location, in which they can expect not to be interrupted.<br>COS will make up to 3 separate attempts to contact the caregiver to |

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| | schedule the interview for a convenient date and time. Should the caregiver not be reached after the third attempt or if a time cannot be scheduled within (or just outside of) the agreed time window, then the caregiver will be considered lost to follow-up.<br>COS will communicate with the sites the interview status (eg, scheduled, completed), and payment request status (eg, payment request sent, payment sent). Once activities are completed (including payment sent to caregiver), COS will inform the site and copy in CRO to confirm the caregiver's completion. |
| Data collection | Interviews will be conducted by experienced interviewers using semi-structured interview guides to facilitate discussion. Interviews in English will be conducted by COS interviewers as scheduling permits. For non-English interviews, or those that cannot be scheduled with COS interviewers, COS will train third-party interviewers on the aims of the study and the interview guide, to ensure they understand the focus and rationale.<br>All interviews will be audio recorded, and transcribed verbatim. Interviews conducted in other languages will be transcribed (via a third-party agency) directly into English. All transcripts will be Quality Checked (QC'ed) to remove any identifiable information by trained COS researchers before analysis is undertaken.<br>Patient demographic and clinical health data will be collected for descriptive purposes. Blinded baseline data will be extracted from the clinical trial dataset and shared with COS through a data transfer. This information will include, but is not limited to patient age, gender, race, and ethnicity.<br>. A Data Transfer Agreement (DTA) will be set up by COS to ensure the secure transfer of the data. Outside of this, sites will also be asked to provide brief demographic data for the caregiver participants. This will be inputted into caregiver contact form shared between COS and trial sites. COS will assign a Caregiver ID that is linked to the participants Clinical Trial ID to allow for comparative data analysis. |
| Analyses | All QC'ed transcripts will be entered into NVivo, a software package which is designed to facilitate the systematic review, coding, and analysis of qualitative data.<br>The data gathered from the sub-study interviews will be subject to thematic analysis and any patterns in the data will be noted. A codebook will be developed which will enable themes to be identified as they emerge from the coded data, which will facilitate the interpretation of data in a manner that addresses relevant project objectives.<br>Demographic and clinical information relating to each subject will be |

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| | provided by Takeda/CRO. This information will be summarized by COS. The tables will be generated using Statistical Analysis System (SAS) Version 9.3 or higher. This data will be summarized to characterize the sample and provide context to the qualitative data from the interviews.<br>COS will develop a qualitative analysis plan outlining the analyses that will be performed to meet the study objectives. This will be an agreement between COS and Takeda about how qualitative data analyses are to be conducted and how data will be presented in the final sub-study reports. |
| Ethical considerations | This sub-study is included in the ENDYMION 2 protocol and is described in the study synopsis as the "caregiver qualitative input sub-study." The ENDYMION 2 protocol states that this is an optional sub-study to be conducted at selected sites. Conduct of these interviews will be considered as an optional procedure of the clinical trial and reviewed/approved by the appropriate ethics committee as such.<br>This study will be conducted in compliance with Good Clinical Practice, including International Conference on Harmonization Guidelines and consistent with the most recent version of the Declaration of Helsinki. In addition, all applicable local laws, and regulatory requirements will be followed where applicable. |
| Reporting adverse event (AE) and serious adverse events (SAEs) | The interviews will not specifically generate or evaluate data on AEs or SAEs associated with the ENDYMION 2 study. However, if a caregiver spontaneously reports an experience that requires documentation as a potential AE or SAE, the interviewer will comply with Takeda specific training and report the event to the site's study investigator within one business day (in the event of a potential AE) or within 24 hours (in the event of a potential SAE). The site investigator receiving the AE will need to reconcile with previous trial information as to whether the potential AE was previously reported (eg, during a prior study visit). The study investigator is responsible for making a determination about the potential AE/SAE and following up with the participant as appropriate.<br>Interviewers will also need to copy in the COS study coordinator into any emails relating to a potential AE or SAE. |

## Appendix J Protocol History

| Date | Amendment Number | Amendment Type (for regional Europe purposes only) | Region |
|---|---|---|---|
| 28 February 2023 | Amendment 2 | Substantial | Global |
| 24 February 2023 | Amendment 1 DE v1 | Substantial | Germany |
| 02 November 2021 | Amendment 1 | Substantial | Global |
| 06 July 2021 | Initial version | Not applicable | Global |

### Rationale for Amendment 1 DE v1

See Section 1.3 for the summary of changes made in Amendment 1 DE v1.

### Rationale for Amendment 1

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to account for potential gaps that may occur between the time the subjects are ready to roll over from the antecedent study (TAK-935-3001 or TAK-935-3002) and the time sites are ready for such subjects in this protocol.

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 1** | | | |
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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*** |
| 1 | Section 1.3, Administrative information | Addition of this section, per Takeda template. | To describe amendment |
| 2 | Section 2.0, Study Summary<br>Section 5.2.1, Primary Endpoints—Safety | Added change from baseline safety laboratory test values, vital signs, and ECG evaluations; other minor rewording | Clarification |
| 3 | Section 2.0, Study Summary<br>Section 5.2.1, Primary Endpoints—Safety<br>Section 9.1.7.3, Procedures for Clinical Laboratory Samples<br>Appendix A, Schedule of Study Procedures | Corrected Tanner staging for subjects ages 6 (not 10) to 17 years<br>Added insulin-like growth factor 1 (IGF-1) collected for subjects ages 2 to 17 years | Lower age to ensure earlier cases of precocious puberty are detected (Tanner staging) and safety monitoring on growth for younger subjects (IGF-1) |
| 4 | Section 2.0, Study Summary<br>Section 6.1, Study Design<br>Section 6.2.1, Study Design<br>Section 7.1, Inclusion Criteria | Modify the minimum treatment requirement in the antecedent study from 10 to 12 weeks (combined titration and Maintenance Period) | In clinical practice, 3 months is usually considered as the minimum time to evaluate the effect of an antiseizure medication |

| **Protocol Amendment 1** | | | |
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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*** |
| 5 | Section 4.1, Background | Remove LGS from the statement about murine models: "Nonclinical studies have demonstrated that soticlestat modulates glutamatergic signaling and significantly reduces spontaneous seizures in murine models of DS~~ and LGS~~." | Finding only applies to Dravet syndrome (DS) |
| 6 | 6.1.1, Dose Titration Period (2 Weeks) | Define times and criteria for safety follow-up phone calls during dose titration | Clarification |
| 7 | Section 6.1.3, Study Discontinuation/Completion | Seizure diary should be maintained through the follow up phone call | Clarification |
| 8 | Section 6.1, Study Design<br>Section 6.1.4, Overall Schedule of Study Assessments<br>Section 9.4.1, Collection of Plasma Samples for Soticlestat PK Evaluation<br>Appendix A, Schedule of Study Procedures | Listed procedures that need (or do not need) to be repeated at the beginning of this study if rollover from the antecedent study is not on the same day, as well as relevant visit and timeframe criteria. | Clarifies what to do if there is a gap between the antecedent study and this study |
| 9 | Section 7.1, Inclusion Criteria | Additional contraceptive methods added to the definition of effective contraception (partner with male condom, combined or progestogen-only hormonal contraception, intrauterine device, and intrauterine hormone-releasing system); removed progestogen only contraception plus condom as an effective contraceptive method | Flexibility for subjects |
| 10 | Section 9.1.4, Vital Sign, Height, And Weight Procedures | Moved procedure for collecting height and weight data to this section | Clarification |
| 11 | Section 9.1.5, Physical Examination Procedure | Described when to perform Tanner staging | Clarification |
| 12 | Section 9.1.7.3, Procedures for Clinical Laboratory Samples<br>Appendix A, Schedule of Study Procedures | Add approximate maximum volume of blood collected at any single visit and approximate total volume of blood collected during the study | Health authority request |
| 13 | Section 9.1.11, Seizure Frequency | Added section to define seizure types and use of seizure and medication diary | Clarification |

| **Protocol Amendment 1** | | | |
|---|---|---|---|
| **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*** |
| 14 | Section 9.1.15, Optional Caregiver Qualitative Input Substudy | Delete 'US-based' from description of substudy | Correction |
| 15 | Section 9.4.4, PD Measurements | Clarified baseline for pharmacodynamic measures | Clarification |
| 16 | Section 10.2.1.1, AE Collection Period | Corrected definition of AE collection period | Correction |
| 17 | Appendix A, Schedule of Study Procedures | Added urine sample collection<br>Added pharmacokinetic and pharmacodynamic plasma samples on Day -1<br>Added row for IGF-1<br>Added 'Dispense study drug' on Day -1 and removed 'Dispense study drug' on Day 7<br>Removed 'Study drug return for compliance/accountability' and 'Collect medication and seizure diary' on Day 7<br>Added 'Collect medication and seizure diary' | Correction |
| 18 | Appendix C, Trial Management During COVID-19 Pandemic | Clarify when virtual visits are allowed | Clarification |

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

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| PPD | Clinical Science Approval | 02-Mar-2023 00:52 UTC |
| PPD | Biostatistics Approval | 02-Mar-2023 01:31 UTC |