Clinical Study Protocol

NCT Number: NCT06422377

Title: An Open-label, Nonrandomized, Phase 3 Study to Evaluate the Efficacy and Safety of Soticlestat in Participants With Dravet Syndrome or Lennox-Gastaut Syndrome Who Have Been Exposed to Fenfluramine.

Study Number: TAK-935-3004

Document Version and Date: Amendment 1.0, 27 June 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

An Open-label, Nonrandomized, Phase 3 Study to Evaluate the Efficacy and Safety of Soticlestat in Participants With Dravet Syndrome or Lennox-Gastaut Syndrome Who Have Been Exposed to Fenfluramine

Brief Title

A Study Evaluating Soticlestat in Participants Who Have Been Exposed to Fenfluramine

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	TAK-935-3004		
Study Phase:	Phase 3		
IND Number:	133627	**Abbreviated EU CT Number:**	2023-504104-29
Investigational Product:	Soticlestat		
Date:	27 June 2023	**Version/Amendment Number:**	Amendment 1

APPROVALS

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 of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES OF THE RESPONSIBLE TAKEDA MEDICAL OFFICER AND OTHER SIGNATORY(IES)

Electronic signatures of the following individuals are provided on the last page of this document.

[redacted], MD, MPH [redacted] Clinical Science Neuroscience Takeda <Date>
[redacted], PhD [redacted] Statistical and Quantitative Sciences Takeda <Date>

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator as described in this protocol.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a potential participant to obtain their informed consent to participate.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Signature of Investigator	Date
Investigator Name (print or type)	
Investigator's Title	
Location of Facility (City, State/Province)	
Location of Facility (Country)	

SUMMARY OF CHANGES

Protocol Amendment 1			
Amendment Date: 27 June 2023			Global/Region/Country/Site Specific: Global
Overall Reason for the Amendment: Minor updates for protocol clarification/correction.			
Description of Each Change and Rationale			**Section(s) Affected by Change**
Change #	**Description of Change**	**Rationale for Change**	**Section**
1.	Revised inclusion criterion #9 in the synopsis to align with the protocol body (Section 5.1).	Inclusion criterion #9 in the synopsis was inadvertently written incorrectly.	Section 1.1
2.	Revised text regarding home visits to be at the discretion of the investigator.	Home visits should be conducted at the discretion of the investigator.	Section 1.3 Section 4.1 Appendix 3
3.	Revised text regarding video calls.	Revised for clarification on use of video calls, particularly during home visits.	Section 4.1
4.	Removed reference to serum pregnancy test.	Revised text for clarification as per Schedule of Activities, which specifies only that urine pregnancy tests are requested; additional pregnancy tests (serum or urine) may be performed throughout the study at the investigator's discretion.	Section 8.3.6
5.	Added "soticlestat program" to Data Monitoring Committee text.	Added to clarify that although there is no data monitoring committee for this study, there is a data monitoring committee for the soticlestat program.	Section 10.1.12.2
6.	Removed alpha-1 acidic glycoprotein from list of tests required for each laboratory specimen.	Alpha-1 acidic glycoprotein will not be included as part of clinical chemistry.	Section 10.2, Table 10.a
7.	Revised the description of calculations in the section on sample size determination	The supporting calculation was updated.	Section 9.8
See Section 10.9 for protocol history, including all previous amendments.			

ADMINISTRATIVE INFORMATION

CONTACTS

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

Takeda sponsored investigators will be provided with emergency medical contact information cards to be carried by each participant, per individual country requirements.

ADDITIONAL INFORMATION

The study operations manual contains additional contact information for:

- Medical monitor, for medical advice on the protocol and the study drug.
- Sponsor's responsible medical officer.
- Monitor assigned to the study site, for general advice on protocol procedures.
- Serious adverse event (SAE) reporting, adverse event of special interest (AESI).
- Special Situation Reporting (SSR) reporting forms.
- Pregnancy reporting.

PRODUCT QUALITY COMPLAINTS

A product quality complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product, device, or combination product after it is released for distribution.

Report product complaints using the form called "Clinical Trial Material Complaint Form."

Send it to the following email address:

ctmcomplaint@takeda.com

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor(s): Takeda Development Center Americas, Inc.		**Compound:** TAK-935	
Study Number: TAK-935-3004	**Phase:** 3	**IND No.:** 133627	**Abbreviated EU CT No.:** 2023-504104-29
Title of Protocol: An Open-label, Nonrandomized, Phase 3 Study to Evaluate the Efficacy and Safety of Soticlestat in Participants With Dravet Syndrome or Lennox-Gastaut Syndrome Who Have Been Exposed to Fenfluramine.			
Short Title: A Study Evaluating Soticlestat in Participants Who Have Been Exposed to Fenfluramine			
Number of Participants: This study plans to enroll approximately 45 participants; 15 participants with Dravet syndrome [DS] and 30 participants with Lennox-Gastaut syndrome [LGS], approximately.			
Investigator(s): Multicenter study			
Site(s) and Region(s): United States, Europe			
Study Period (Planned): Q4 2023 to approximately Q1 2026			
Objectives and Endpoints:			
Objectives **Primary Objective** To assess the efficacy of soticlestat in participants with DS or LGS who have been exposed to fenfluramine. **Exploratory Objectives** • To explore effects of soticlestat on seizure frequency, quality of life and non-seizure symptoms in participants with DS or LGS who have been exposed to fenfluramine. • To explore safety and tolerability of soticlestat in participants with DS or LGS who have been exposed to fenfluramine.			
Endpoints **Primary Endpoint:** Percent change from baseline in convulsive (DS) and major motor drop (MMD) (LGS) seizure frequency per 28 days during the initial 12 weeks of the maintenance period. **Exploratory Endpoints:** • Percent change from baseline in convulsive (DS) /and MMD (LGS) seizure frequency per 28 days during every 12 weeks after the initial 12 weeks of the maintenance period. • Percent change from baseline in convulsive (DS) and /MMD (LGS) seizure frequency per 28 days during the initial 16 weeks of the treatment period (4 weeks of titration + initial 12 weeks of maintenance). • Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 12 weeks of the maintenance period. • Percent change from baseline in total seizure frequency per 28 days of all seizure types during every 12 weeks after the initial 12 weeks of the maintenance period.			

- Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 16 weeks of the treatment period (4 weeks of titration + initial 12 weeks of maintenance).
- Percent change from baseline in seizure frequency per 28 days of each seizure type identified at the time of screening or baseline during the maintenance period and full treatment period (52 weeks).
- Treatment response as defined by ≥50% reduction in convulsive (DS) and MMD (LGS) seizure frequency per 28 days from baseline every 12 weeks after the initial 12 weeks of the maintenance period.
- Treatment response as defined by ≥50% reduction in convulsive (DS) and MMD (LGS) seizure frequency per 28 days from baseline during the initial 16 weeks of the full treatment period (4 weeks of titration period + initial 12 weeks of maintenance period).
- Clinical Global Impression of Improvement (CGI-I) (clinician).
- Caregiver Global Impression of Improvement (Care GI-I).
- CGI-I Seizure Intensity and Duration.
- CGI-I Non-seizure Symptoms completed by clinician with input from the caregivers.
- Quality of Life Inventory-Disability (QI-Disability).
- Change in EQ-5D 5-level version (EQ-5D-5L) and EQ-5D visual analogue scale (EQ VAS) scores.
- Caregiver satisfaction questionnaire.
- Days when rescue anti-seizure medication (ASM) is used.
- The safety endpoints include
  - Incidence of treatment- emergent adverse events (TEAEs).
  - Columbia-Suicide Severity Rating Scale (C-SSRS).
  - Ophthalmological evaluations.

Rationale:

Currently, soticlestat is being studied in 2 global phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group studies in approximately 234 participants with LGS and 142 participants with DS. These studies will evaluate efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in participants with DS and LGS and are expected to be completed during the TAK-935-3004 study.

A multisite, phase 3, open-label extension (OLE) study TAK-935-3003 (ENDYMION 2) is ongoing to obtain additional safety and tolerability data related to soticlestat administered long-term in participants who participated in either of the antecedent phase 3 clinical studies, TAK-935-3001 (participants with DS) or TAK-935-3002 (participants with LGS).

The TAK-935-3004 study is specifically designed to obtain additional clinical efficacy, safety and tolerability data in participants who have been exposed to fenfluramine. In clinical practice ASMs are generally added on as standard of care. Because fenfluramine is expected to be part of standard of care ASM regimens but is not widely used in current clinical practice due to its recent approval in the European Union, we propose this study to evaluate soticlestat in participants with DS and LGS, who are previously or currently exposed to fenfluramine.

There are no pharmacokinetic or pharmacodynamic interactions expected by combining soticlestat with fenfluramine.

Study Drug, Dose, and Mode of Administration:

In this study, the study drug is soticlestat.

The total daily dose of soticlestat will be calculated based on body weight at Visit 1 (screening visit) and given twice a day (BID). The minimum dose allowed during the study is 100 mg BID (or 100 mg BID equivalent weight-based dosing for weight <45 kg). Participants weighing <45 kg will be dispensed 20 mg mini-tablets, if appropriate. Participants weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets. The maximum allowed dose is 300 mg BID. Intermediate doses between dose levels may be allowed after discussion with medical monitor.

Overall Design and Methodology:

This is a phase 3, open-label, nonrandomized, single-arm study in participants with DS or LGS who have been exposed to fenfluramine.

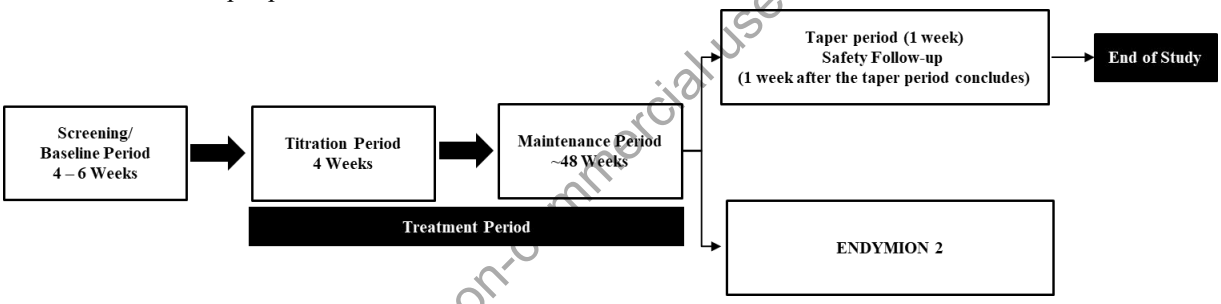
"Exposure" is defined as participants who are current or prior users of fenfluramine

Note: Participants who have discontinued fenfluramine for reasons of lack of efficacy or intolerability are eligible as prior users.

Approximately 15 participants with DS and 30 participants with LGS will be enrolled in the study.

The study will consist of the following periods:

- A 4- to 6-week screening/baseline period.
- Approximately 52-week full treatment period including:
  - A 4-week titration period.
  - Approximately 48-week maintenance period.
- A 1-week taper period for those discontinuing study drug (participants not entering the phase 3 OLE study ENDYMION 2).
- A safety follow-up visit or a phone call (participants not entering ENDYMION 2) to occur approximately 1 week after the taper period concludes.



The total daily dose of soticlestat will be calculated based on body weight at Visit 1 (screening visit) and given twice daily (BID). Participants will receive the initial dose of the study drug, ie. Dose 1 (100 mg BID adult reference dose, weight-based dosing for weight <45 kg) for the first 7 days of the dose titration period.

Approximately 7 days after starting Dose 1, study drug dose will be increased to Dose 2 (200 mg BID adult reference dose, weight-based dosing for weight <45 kg) and continued for approximately 7 days. Seven days after receiving Dose 2, drug dose can be increased to Dose 3 (300 mg BID adult reference dose, weight-based dosing for weight <45 kg). If the participants do not experience any tolerability issues, they will remain on the Dose 3 for the remainder of the titration period, followed by a safety follow-up phone call.

The minimum dose allowed during the study is 100 mg BID (weight-based dosing for weight <45 kg). Participants who cannot tolerate the minimum dose will be discontinued from the study. The dose may be decreased during the initial 12 weeks of maintenance period for safety or tolerability issues based on investigator clinical judgment. After the initial 12 weeks of maintenance period, intermediate doses between dose levels may be allowed after discussion with medical monitor.

The final dose tolerated by the end of the 4-week titration period should be maintained during the first 12 weeks of the maintenance period unless tolerability issues arise.

ASMs taken as standard of care, should remain stable for initial 12 weeks of the maintenance period, after which, doses can be adjusted based on standard of care and investigator judgement.

Rescue medication dose can be adjusted throughout the study per standard of care (SOC).

After the initial 12 weeks of maintenance period, dose of soticlestat can be adjusted according to participant weight changes and investigator judgement. At the end of the overall maintenance period, participants will have the option to enroll in the OLE study ENDYMION 2 at the same dose they were on in TAK-935-3004, as deemed

appropriate by the investigator.

For participants not entering ENDYMION 2, the dose will be tapered for approximately 1 week (unless already at the lowest dose), followed by a safety follow-up visit or phone call approximately 2 weeks after the final visit/early termination.

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).

In prior studies, soticlestat was generally well tolerated in participants with developmental epileptic encephalopathies at doses up to 300 mg BID (with titration) of adult equivalent dose.

Given the severe, profound, and chronic nature of DS and LGS, associated signs and symptoms, and 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 in these populations.

The phase 2 study, ELEKTRA showed that soticlestat treatment resulted in a significant median percent reduction from baseline in convulsive (DS) and MMD (LGS) seizure frequency compared with placebo in the combined population of DS and LGS during the maintenance period. It also showed statistically significant median percent reduction from baseline convulsive seizure frequency in participants with DS compared with placebo as well as a directional median percent reduction from baseline in drop seizure frequency in participants with LGS. Soticlestat was generally well tolerated, with findings consistent with those from previous studies. We will further evaluate these findings in participants who were exposed to fenfluramine in this study.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. In the opinion of the investigator, the participant or the participant's parent or legal guardian or caregiver is capable of understanding and complying with protocol requirements, complete appropriate assessments, maintain an accurate and complete daily seizure diary and take study drug for the duration of the study.

   If the participant is living in a residential facility, a minimally possible number of staff member(s) at the facility who are the participant's primary caretaker(s) may be identified as caregivers who (per investigator's judgement) are capable of complying with protocol requirements as indicated above.
2. The participant/participant's legally acceptable representative has provided informed consent (that is, in writing, documented via a signed and dated informed consent form) and any required privacy authorization before the initiation of any study procedures.
3. The participant, of any sex, aged ≥2 years, at the time of informed consent.
4. The participant has a documented clinical diagnosis of DS supported by variable combinations of typical clinical features such as those noted as follows and as determined by the investigator.
   - Onset of seizures usually in the first year of life.
   - History of fever-induced prolonged seizure as determined by the investigator
   - May include prolonged (approximately 15 minutes or longer) hemi-clonic seizures.
   - Multiple seizure types, which may include:
     - Generalized tonic-clonic.
     - Focal to bilateral tonic-clonic.
     - Clonic.

- Myoclonic

– History of developmental delay/intellectual disability presenting after onset of seizures and usually presenting after 12 months of age.

– Documented genetic mutation consistent with DS is not required, but results of genetic testing will be collected if available. If genetic testing was not performed previously or if the *SCN1A* result is negative (without any other positive gene reported that is consistent clinically with DS), testing for *SCN1A* will be offered at the time of screening, per local restrictions.

OR

The participant has a documented clinical diagnosis of LGS supported by variable combinations of typical clinical features such as those noted as follows and as determined by the investigator.

– Onset of seizures usually between the ages of 1 and 8 years.

– Presence of multiple seizure types: including drop seizures (eg, tonic-atonic seizures) and other seizure types including atypical absence seizures, tonic-clonic, myoclonic, and partial seizures.

– History of abnormal electroencephalogram (EEG) results (eg, slow spike and wave [<2.5 Hz], slow or disorganized EEG background, generalized paroxysmal fast activity).

– Developmental delay or intellectual disability consistent with LGS.

5. The participant has experienced failure of treatment to control seizures despite appropriate trials of at least 1 ASM based on historical information and is currently on an antiseizure therapy (eg, ASMs, vagus nerve stimulation [VNS], ketogenic/modified Atkins diet) or other treatment options considered as SOC.
6. The participant has been exposed to fenfluramine (currently on or used previously).

   Note: Participants, who have discontinued fenfluramine for reasons of lack of efficacy or intolerability are eligible as prior users.
7. The participant has a clinical diagnosis of LGS and a history of, on average, ≥12 MMD seizures in the last 90 days immediately before screening based on historical information, and the participant has ≥4 MMD seizures during a minimum of 4 weeks of seizure data collection during the prospective baseline period.

   The total number of seizures includes only primary outcome seizure types with documentation as determined by the investigator:

   – Hemi-clonic or focal clonic.
   – Focal to bilateral tonic-clonic.
   – Generalized tonic-clonic.
   – Bilateral clonic.
   – Convulsive status.
   – Focal 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.

   OR

   The participant has a clinical diagnosis of DS and a history of, on average, ≥9 convulsive seizures in the last 90 days before screening visit based on the historical information, and the participant has ≥3 convulsive seizures during a minimum of 4 weeks of seizure data collection during the prospective baseline period.

   The total number of seizures includes only primary outcome seizure types with documentation as determined by the investigator:

- Hemi-clonic or focal clonic.
- Focal to bilateral tonic-clonic.
- Generalized tonic-clonic.
- Bilateral clonic.
- Convulsive status.

8. The participant weighs ≥10 kg at the screening visit (Visit 1).
9. Artisanal cannabidiols/nonpharmaceutical grade cannabidiols are allowed. Participants should be on a stable dose for at least 4 weeks before the screening visit (Visit 1); the dosing regimen and manufacturer should remain constant during the initial 16 weeks of treatment period (including 4 weeks of titration period and 12 weeks of maintenance period) of the study. (Artisanal cannabidiols will not be counted as ASMs.)
10. The participant is currently taking 0 to 5 antiseizure treatments (eg. VNS, ketogenic diet) at stable doses, of which:
    a) Four can be ASMs, before the screening visit (Visit 1); benzodiazepines used chronically (daily) to treat seizures are considered ASMs. Cannabidiol (Epidiolex) is allowed where available and should be counted as an ASM. ASM dosing regimen must remain constant during the initial 16 weeks of treatment period (4 weeks of titration + initial 12 weeks of maintenance).
    b) If using a VNS, the participant must have had VNS placed at least 3 months before the screening visit (Visit 1) with stable settings for at least 4 weeks before the screening visit (Visit 1); VNS parameters must remain constant during the initial 16 weeks of treatment period (4 weeks of titration + initial 12 weeks of maintenance) of the study.
    c) If on a ketogenic diet (or any other diet used for treatment of epilepsy, such as modified Atkins diet), the participant must have started the diet at least 3 months before the screening visit (Visit 1), and the participant's diet should be stable for 4 weeks before the screening visit (Visit 1); the participant should continue this diet during the initial 16 weeks of treatment period (4 weeks of titration + initial 12 weeks of maintenance) of the study.
11. The use of felbamate is allowed provided that the participant does not meet the liver function test exclusion criteria, the dose has been stable for at least 6 months before the screening (Visit 1), and the participant has had stable liver function (as determined by serum aspartate aminotransferase and alanine aminotransferase levels) and hematology laboratory tests during the course of treatment.
12. Participants 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 (as defined in this protocol) during the study and for 30 days following the last dose of study drug.

Exclusion Criteria:

1. The participant is not an investigator site personnel directly affiliated with this study and/or their immediate family.

   Note: Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
2. The participant is not Takeda employee or immediate family member.
3. The participant is currently enrolled in a clinical study involving an investigational product or treatment device (ie, not approved in that country, other than soticlestat), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

   Note: Compatibility will be determined on the basis of consultation with the sponsor/designee.
4. The participant has participated in a clinical study involving another study drug in the last 30 days (or 5 half-lives of the study drug, whichever is longer) before screening (Visit 1).
5. The participant has a known hypersensitivity to any component of the soticlestat formulation.

6. The participant has an 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 sponsor/designee may be warranted.
7. The participant has any history of alcohol, opioid, or other drug use disorder, per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, within 2 years of the screening visit (Visit 1).
8. The participant is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the participant has attempted suicide within 12 months before the screening visit (Visit 1). Participants aged ≥6 years who have positive answers on item numbers 4 or 5 on the C-SSRS before dosing (Visit 2) are excluded. This scale will only be administered to participants aged ≥6 years at the time of enrollment or participants who turn 6 after enrollment.
9. The participant is unable to withhold the use of strong inducers of cytochrome P450(CYP 3A4) during the entire clinical study, (except for ASMs [eg, carbamazepine, phenobarbital, phenytoin] and topical preparations).
10. The participant is currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug.

Drug Groups and Duration, Including Maximum Duration of Participant Involvement in the Study:

The total duration of study participation for each participant includes:

Planned duration of screening period: 4 to 6 weeks

Planned duration of enrollment/treatment period: Approximately 4 weeks of titration period and 48 weeks of maintenance period.

Planned duration of follow-up: 2 weeks (if not enrolled into ENDYMION 2)

Statistical Analysis:

Safety analysis set: All participants who take at least 1 dose of study drug.

Intent-to-treat (ITT) analysis set: All participants who enroll in the study.

Modified intent-to-treat (mITT) analysis set: All enrolled participants who take at least 1 dose of study drug and are assessed for seizures for at least 1 day in the treatment period.

Efficacy analyses will be performed using the mITT analysis set. Results will be presented separately for the DS and LGS cohorts using descriptive statistics.

For all efficacy analyses on seizure frequency, baseline refers to the prospective 4- to 6-week screening/baseline period.

Percent change from baseline in primary seizure frequency (convulsive for DS and MMD for LGS) per 28 days during the initial 12 weeks of the maintenance period will be summarized using descriptive statistics including mean, median, SD, first quartile, third quartile, minimum, and maximum. A distribution-free 95% CI for the median will be presented.

Other percent change from baseline in seizure frequency endpoints will be summarized similarly to the primary endpoint. Percent change from baseline in seizure frequency (convulsive for DS and MMD for LGS) per 28 days and total seizure frequency per 28 days will be summarized for the initial 16 weeks of the treatment period (4 weeks of titration + initial 12 weeks of maintenance), and every 12-week period thereafter.

Descriptive summaries of CGI-I, Care GI-I, CGI-I Seizure Intensity and Duration, CGI-I Nonseizure Symptoms, QI-disability, caregiver satisfaction, and EQ-5D-5L will be presented for each scheduled collection time point and at end of study. 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. Other binary endpoints will be summarized in a similar

fashion, as appropriate.

The EQ VAS score and the total score for QI-Disability will also be summarized in terms of change from baseline at each collection time point. EQ-5D-5L will be summarized descriptively by visit including baseline by presenting the number and percentage of responses in each level within each dimension.

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

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

Analyses will be based on as-observed data. No imputation will be implemented. Baseline assessment for efficacy analyses other than seizure is the assessment prior and closest to the first administration of the study drug unless otherwise specified.

Interim data cuts from this ongoing study will be analyzed to support any regulatory submissions. Since there is no hypothesis testing involved, no interim analysis will require spending any type-I error.

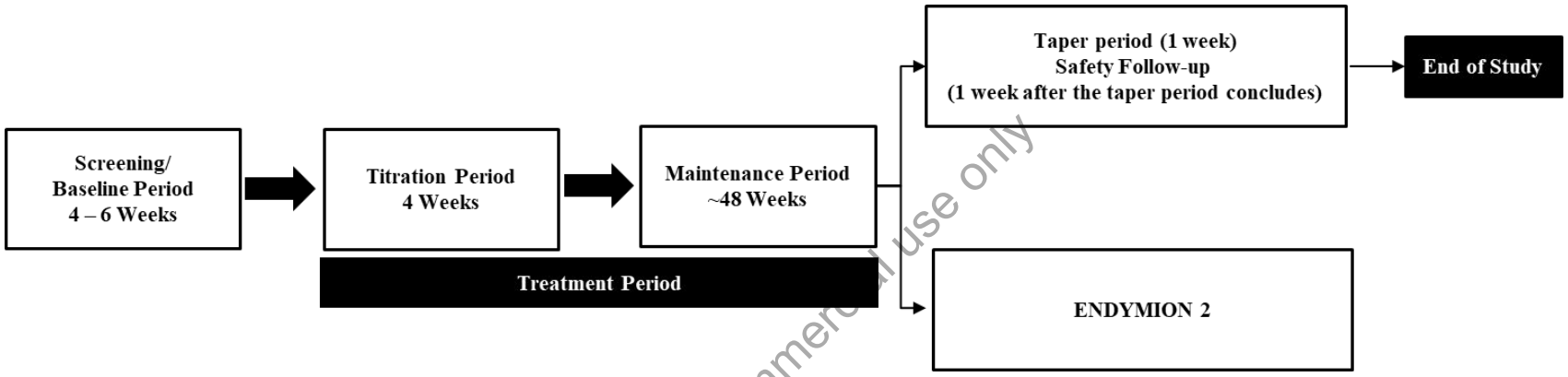
Safety analyses will be performed using the safety analysis set. Results will be presented descriptively. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. TEAEs will be summarized using Preferred Terms and primary System Organ Classes.

Data summaries will be displayed for incidence of TEAEs, clinical laboratory variables, and vital sign parameters. Ophthalmological evaluations and C-SSRS will be listed by participant.

Data Monitoring/Other Committee: No

1.2 Schema

Figure 1.a Study Schema



1.3 Schedule of Activities

Table 1.a Schedule of Activities

Study Procedure	Screening/ Baseline Period [b, c]	Enrollment day [b, c, h]	Open-label Treatment: Full Treatment Period = 52 weeks [a, b] — Titration Period [d] (4 weeks)				Maintenance Period (~48 weeks) [e]						Taper Period (~1 week) [f]	Safety Follow-up (1 week) [b, f]
Study Day [g]	Days -43/ -29 to -2	Day -1	Day 1 (Titration Dose 1) [i, j, k, l]	Day 8 (Titration Dose 2) [i, j, k, l]	Day 15 (Titration Dose 3) [i, j, k, l]	Day 28 (End of Titration)	Day 29 [h]	Day 56 [m]	Day 112	Day 196 [i]	Day 280 [i]	Day 364/ ET [n, o, p]		Day 378 [i]
Visit Window (days)				±2	±2		±7	±10	±7	±14	±14	±14		±7
Visit Number	V1	V2	V3	V4	V5		V6		V7	V8	V9	V10		V11
Informed consent and assent (if applicable)	X													
Collect historical seizure data	X													
Inclusion/exclusion criteria	X	X [q]												
Demographics, medical history, medication history (including ASMs and fenfluramine)	X													
Height, weight	X								X [r]	X [r]	X [r]	X		
Urine pregnancy test [s]	X	X							X	X	X	X		
Vital signs	X								X	X	X	X		
Physical examination	X								X	X	X	X		
Neurological examination	X								X	X	X	X		
Clinical laboratory tests (chemistry, hematology, and urinalysis) [t]	X								X			X		
Ophthalmological examination [u]	X								X			X		

Table 1.a Schedule of Activities

Study Procedure		Open-label Treatment												
			Full Treatment Period = 52 weeks [a, b]											
	Screening/ Baseline Period [b, c]	Enrollment day [b, c, h]	Titration Period [d] (4 weeks)				Maintenance Period (~48 weeks) [e]						Taper Period (~1 week) [f]	Safety Follow-up (1 week) [b, f]
Study Day [g]	Days -43/ -29 to -2	Day -1	Day 1 (Titration Dose 1) [i, j, k, l]	Day 8 (Titration Dose 2) [i, j, k, l]	Day 15 (Titration Dose 3) [i, j, k, l]	Day 28 (End of Titration)	Day 29 [h]	Day 56 [m]	Day 112	Day 196 [i]	Day 280 [i]	Day 364/ ET [n, o, p]		Day 378 [i]
Visit Window (days)				±2	±2		±7	±10	±7	±14	±14	±14		±7
Visit Number	V1	V2	V3	V4	V5		V6		V7	V8	V9	V10		V11
Concomitant medications review	X													
Concomitant ASM and rescue medications	X													
C-SSRS [v]	X	X					X		X			X		
Seizure and medication diary (paper)	X													
CGI-I (clinician) questionnaire							X		X			X		
CGI/Care GI Baseline questionnaire		X [w]												
Care GI-I questionnaire							X		X			X		
CGI Baseline–Nonseizure Symptoms questionnaire		X [x]												
CGI Baseline–Seizure Intensity and Duration questionnaire		X [y]												
CGI-I Nonseizure Symptoms questionnaire (clinician)							X		X			X		
CGI-I Seizure Intensity and Duration questionnaire (clinician)							X		X			X		

Table 1.a Schedule of Activities

Study Procedure	Screening/ Baseline Period [b, c]	Enrollment day [b, c, h]	Open-label Treatment: Full Treatment Period = 52 weeks [a, b] — Titration Period [d] (4 weeks)				Maintenance Period (~48 weeks) [e]						Taper Period (~1 week) [f]	Safety Follow-up (1 week) [b, f]
Study Day [g]	**Days -43/ -29 to -2**	**Day -1**	**Day 1 (Titration Dose 1) [i, j, k, l]**	**Day 8 (Titration Dose 2) [i, j, k, l]**	**Day 15 (Titration Dose 3) [i, j, k, l]**	**Day 28 (End of Titration)**	**Day 29 [h]**	**Day 56 [m]**	**Day 112**	**Day 196 [i]**	**Day 280 [i]**	**Day 364/ ET [n, o, p]**		**Day 378 [i]**
Visit Window (days)				±2	±2		±7	±10	±7	±14	±14	±14		±7
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**		**V6**		**V7**	**V8**	**V9**	**V10**		**V11**
QI-Disability		X							X			X		
EQ-5D-5L quality of life scale	X								X			X		
Caregiver satisfaction questionnaire [z]									X					
Obtain participant ID/medication ID/document participant status	X													
Dispense study drug (BID administration) [aa]		X	X					X [l]	X	X	X	X [f]		
Study drug return, accountability, and compliance [bb]		X												
Adverse events	X													
Genetic testing (*SCN1A*) [cc]	X													

ASM: antiseizure medication; BID: twice daily; Care GI: Caregiver Global Impression; Care GI-I: Caregiver Global Impression of Improvement; CGI: Clinical Global Impression; CGI-I: Clinical Global Impression of Improvement; C-SSRS: Columbia-Suicide Severity Rating Scale; eCRF: electronic case report form; ENDYMION 2: TAK-935-3003; EQ-5D-5L: EQ-5D 5-level version; ET: early termination; hCG: human chorionic gonadotropin: ID: identification (number); QI-Disability: Quality of Life Inventory-Disability.

[a] Participant's care and necessity for on-site visits during the full treatment period will be determined on the basis of the investigator's clinical judgment. Data collection must be performed for every visit (including virtual) per site-specific clinical practice guidelines. Any additional testing clinically required should be collected throughout the study, including laboratory/chemistry results, blood pressure, and information about any treatment change made throughout the study.

[b] Home visits may be conducted by site staff at the discretion of the investigator and if permissible by local regulations.

[c] The investigator is expected not to adjust concomitant ASM(s) as well as calories of ketogenic diet and VNS setting through during the baseline period. The minimum duration for screening is 28 days and maximum is 42 days.

[d] The investigator is expected not to adjust concomitant ASM(s) as well as calories of ketogenic diet and VNS setting during the titration period through the initial 16 weeks of treatment period (4 weeks of titration period + initial 12 weeks of maintenance period).

[e] Dose reductions during the first 12 weeks of the maintenance period are allowed for safety or tolerability reasons only as assessed by the investigator; dose changes will need to be discussed with the sponsor/designee.

[f] Taper period (up to 1 week) and follow-up period (1 week after the taper period concludes) will not be required for participants enrolling in extension study (ENDYMION 2). Follow-up visit to occur approximately 1 week after taper period concludes. Same course to be followed for ET participants.

[g] If the date of a participant visit does not conform to the study plan, the timing of subsequent visits should be planned so that the visit schedule relative to Day 1 is maintained. Note: this does not apply to dose titration days.

[h] Visit is encouraged to be in-person but can be virtual based on investigator judgement. If virtual, investigator should conduct CGI scales via video at minimum. The remaining scales may be conducted via phone.

[i] Virtual visits are allowed if aligned with institutional or local guidelines, via phone or via any platforms approved by local regulations. Participants may be seen at times other than indicated in the schedule of assessments if clinically required.

[j] It is recommended to stabilize participants at the participant's optimal dose level before proceeding to the maintenance period (eg, do not start participants on 300 mg 1 day before the maintenance period). There is no specific requirement to stay at a dose level if not tolerated. Investigator's judgment will be used to determine the optimal dose based on participant's tolerability and response. Taper down procedures including participant monitoring should be followed.

[k] Participants will take the initial dose of study drug (Dose 1) the morning after the enrollment day (Day -1). For participants receiving the study drug at home through courier should take it the morning after they receive it, therefore for these participants Day 1 may not immediately follow Day -1. Dose 2 and Dose 3 are started the evening of dose titration (Day 8 [Visit 4] and Day 15 [Visit 5], respectively).

[l] Approximately 2 days after starting Dose 1 and after each dose change or taper, sites should contact participants by phone to monitor study drug compliance, to assess the tolerability and safety of the study drug, and to monitor concomitant medication use and treatment-emergent adverse events. These safety checks are calculated as approximately 2 days after starting Dose 1, Dose 2, and Dose 3, respectively. Additional monitoring during optimization period is permissible based on investigator's clinical judgement.

[m] This is NOT a study visit, hence, no study procedures will be performed. The study participants are not required to visit. At approximately Day 56, caregivers will return to the site for the purposes of drug dispensing, return of paper diaries and unused study drug.

[n] At Day 364/ET, participants who do not enroll in the extension study (ENDYMION 2) that day will be dispensed study drug to taper down, and they will begin taking the taper down study drug. in the evening of the Day 364/ET visit.

[o] Participants who do not continue into the extension study (ENDYMION 2) will undergo the dose taper procedures and safety follow-up visit/call.

[p] Participants who enroll in the extension study (ENDYMION 2) that day (Day 364/ET) should take their final dose of TAK-935-3004 open-label study drug in the evening of the day of Day 364/ET.

[q] Investigator to sign-off via target eligibility form.

[r] Weight only to be collected at these visits (height is not required).

[s] For participants of childbearing potential, pregnancy test at Visit 2 (Day -1/enrollment) is not required for eligibility if Visit 1 (screening) test is negative and if the investigator does not deem it necessary to repeat pregnancy test at Visit 2 (Day -1/enrollment). Urine hCG pregnancy tests will also be performed at Visit 7, 8, 9, and 10 (Day 364)/ET. Additional pregnancy tests (serum or urine) may be performed throughout the study at the investigator's discretion. The investigator can do a serum hCG test at a local laboratory to confirm any positive urine hCG test.

[t] Clinical laboratory tests can be performed anytime during 4 to 6 weeks of screening period. Unscheduled/retests are allowed at investigator discretion. Volume will not exceed 2.4 mL/kg of body weight during any 4-week period.

[u] These evaluations are to be conducted at baseline (between the screening and enrollment visits), at Day 112 (±2 weeks) and at Day 364 (±1 week) or at the ET visit (±1 week) for those participants who do not complete the study.

[v] Two versions of the C-SSRS will be used for all participants aged ≥6 years. The C-SSRS Children's Screening/Baseline (recall period lifetime/12 months) will be completed at the screening (Visit 1) and the C-SSRS Children's Since-Last-Visit at subsequent visits. Children who are younger than 6 years at the start of the study will have an unscheduled visit after turning age 6 years, at which time the C-SSRS Children's Screening/Baseline version will be completed. The C-SSRS Children's Since-Last-Visit version will be completed at the end of the study.

[w] For assessing baseline Care GI and overall CGI (clinician), the clinician will interview the caregiver and complete the CGI Baseline–Care GI Baseline questionnaire provided by the sponsor. The clinician will use this same questionnaire to record their own CGI baseline assessment. This is for the clinician and caregiver's reference for completing the CGI-I (clinician only) and Care GI-I after baseline and hence responses may not be required to be recorded in eCRF.

[x] For assessing baseline CGI-I Nonseizure Symptoms, site rater will complete the CGI Baseline–Nonseizure Symptoms questionnaire provided by sponsor instead of the CGI-I Nonseizure Symptoms scale. This is to be completed by the clinician and for the clinician's reference for completing the CGI-I Nonseizure Symptoms after baseline and hence responses may not be required to be recorded in eCRF.

[y] For assessing baseline CGI-I Seizure Intensity and Duration, site rater will complete the CGI Baseline–Seizure Intensity and Duration questionnaire provided by the sponsor instead of the CGI-I Seizure Intensity and Duration scale. This is to be completed by the clinician and for the clinician's reference for completing the CGI-I Seizure Intensity and Duration after baseline and hence responses may not be required to be recorded in eCRF.

[z] A questionnaire to be provided to caregiver for completion to assess overall satisfaction with soticlestat.

[aa] The dispensing of study drug (soticlestat) will be performed at the enrollment visit (Visit 2), approximately Day 56 (Week 8), Day 112 (Week 16) and then every 3 months. If additional study drug needs to be dispensed, enter as an unscheduled visit. Note: Site may not courier study drug to participants in locations where it is not permitted.

[bb] The investigator will determine the frequency and timing of study drug (soticlestat) return, compliance, and accountability.

[cc] For participants with DS only: If genetic testing was not performed previously or if the *SCN1A* result is negative (without any other positive gene reported that is consistent clinically with DS), testing for *SCN1A* will be offered at the time of screening, per local restrictions.

2.0 INTRODUCTION

2.1 Study Rationale

Currently, soticlestat is being studied in 2 global phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group studies in approximately 234 participants with Lennox-Gastaut syndrome (LGS) and 142 participants with Dravet syndrome (DS). These studies will evaluate efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in participants with DS and LGS and are expected to be completed during the TAK-935-3004 study.

A multisite, phase 3, open-label extension (OLE) study TAK-935-3003 (ENDYMION 2) is ongoing to obtain additional safety and tolerability data related to soticlestat administered long-term in participants who participated in either of the antecedent phase 3 clinical studies, TAK-935-3001 (participants with DS) or TAK-935-3002 (participants with LGS).

The TAK-935-3004 study is specifically designed to obtain additional clinical efficacy, safety and tolerability data in participants who have been exposed to fenfluramine. In clinical practice antiseizure medications (ASMs) are generally added on as standard of care (SOC).

There are no pharmacokinetic (PK) or pharmacodynamic (PD) interactions expected by combining soticlestat with fenfluramine.

Due to its recent approval in the European Union (EU), fenfluramine is not widely used in current clinical practice, although it is expected to be part of the SOC ASM regimens. This study evaluates soticlestat in participants with DS and LGS, who are currently or previously exposed to fenfluramine.

2.2 Background

DS or severe myoclonic epilepsy in infancy is one of the best described disorders of epileptic encephalopathies. Clinically, DS is characterized at onset by frequent convulsive febrile seizures, followed later by frequent status epilepticus and nonfebrile seizures that are mainly clonic, unilateral, and of long duration (Dravet 2011).

LGS is rare and 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 in adulthood. LGS includes the presence of multiple seizure types: including 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 24*S*-hydroxycholesterol (24HC) and improve convulsive seizure control in participants with DS and major motor drop (MMD) seizure control in participants with LGS.

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 participants with DS or LGS. ELEKTRA was a phase 2, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy, safety, tolerability, PK, and PD of soticlestat as adjunctive therapy in pediatric participants aged ≥2 and ≤17 years with LGS or DS. A total of 141 participants were enrolled (51 with DS and 90 with LGS), and 126 completed the study. Participants 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). Participants who met the entry criteria were stratified by syndrome and randomized in a 1:1 ratio to soticlestat or matching placebo within each cohort. Participants 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. Participants weighing <60 kg received weight-based equivalent doses.

In the DS cohort (N = 51), participants treated with soticlestat demonstrated a 33.8% median reduction in convulsive seizure frequency compared with a 7.0% median increase seen in participants 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 participants 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% compared with a median decrease of 6% in the placebo group (median placebo-adjusted reduction in 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 participants with DS and LGS showed improvement than those receiving placebo (26.9% vs 8% and 27.9% vs 11.1%, respectively) as deemed by the investigator.

Caregivers also rated greater improvement in 57.7% and 51.2% of soticlestat-treated participants with DS and LGS 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 participants (80.3%) who received soticlestat experiencing at least 1 TEAE compared with 52 participants (74.3%) who received placebo. 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 participants with ≥5% difference from placebo were lethargy and constipation. The incidence of serious TEAEs was similar in both soticlestat and placebo groups, with 11 participants (15.5%) in the soticlestat group experiencing at least 1 serious TEAE compared with 13 participants (18.6%) in the placebo group. Four participants (5.6%) in the soticlestat group discontinued the study due to TEAEs compared with 3 participants (4.3%) in the placebo group.

An open-label study (TAK-935-18-001, ENDYMION 1) of participants with developmental epileptic encephalopathies (DEEs) is currently in progress. In addition to ELEKTRA, participants 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 PD of soticlestat as adjunctive therapy (to antiepileptic drugs) in 18 adult participants diagnosed with a DEE, and TAK-935-18-002 (ARCADE), an open-label, parallel-group study in participants with chromosome 15q duplication syndrome or cyclin-dependent kinase-like 5 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.

2.3 Benefit-Risk Assessment

In the phase 1b/2a TAK-935-2001, phase 2 ELEKTRA, and open-label pilot ARCADE studies, the safety and tolerability data indicate that soticlestat was generally well tolerated in participants 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).

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 participants with DS and LGS.

DS is characterized by treatment-resistant seizures, presenting at a very young age. In addition, mortality is especially high in DS (up to 21%) (Shmuely et al. 2016), even compared with other epilepsy syndromes, with a 30-fold higher rate of sudden unexpected death in epilepsy that accounts for up to 60% of deaths in these patients (Richards et al. 2018). 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, electroencephalogram (EEG) findings, and intellectual impairment.

In prior studies, soticlestat was generally well tolerated in participants with DEEs at doses up to 300 mg BID of adult equivalent dose.

Given the severe, profound, and chronic nature of DS and LGS, their associated signs and symptoms, and 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 in these populations.

The phase 2 study, ELEKTRA showed that soticlestat treatment resulted in a significant median reduction from baseline in convulsive (DS) and MMD (LGS) seizure frequency compared with placebo in the combined population of DS and LGS during the maintenance period. It also showed statistically significant median percent reduction from baseline convulsive seizure frequency in participants with DS compared with placebo as well as a directional median percent reduction from baseline in drop seizure frequency in participants with LGS. Soticlestat was generally well tolerated, with findings consistent with those from previous studies. We will further evaluate these findings in participants who were exposed to fenfluramine in this study.

3.0 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives

To assess the efficacy of soticlestat in participants with DS or LGS who have been exposed to fenfluramine.

3.1.2 Exploratory Objectives

- To explore effects of soticlestat on seizure frequency, quality of life and nonseizure symptoms in participants with DS or LGS who have been exposed to fenfluramine.
- To explore safety and tolerability of soticlestat in participants with DS or LGS who have been exposed to fenfluramine

3.2 Endpoints

3.2.1 Primary Endpoint

Percent change from baseline in convulsive (DS) and MMD (LGS) seizure frequency per 28 days during the initial 12 weeks of the maintenance period.

3.2.2 Exploratory Endpoints

- Percent change from baseline in convulsive (DS) and MMD (LGS) seizure frequency per 28 days during every 12 weeks after the initial 12 weeks of the maintenance period.
- Percent change from baseline in convulsive (DS) and MMD (LGS) seizure frequency per 28 days during the initial 16 weeks of the treatment period (4 weeks of titration period + initial 12 weeks of maintenance period).
- Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 12 weeks of the maintenance period.
- Percent change from baseline in total seizure frequency per 28 days of all seizure types every 12 weeks after the initial 12 weeks of the maintenance period.
- Percent change from baseline in total seizure frequency per 28 days of all seizure types during the initial 16 weeks of the treatment period (4 weeks of titration period + initial 12 weeks of maintenance period).
- Percent change from baseline in seizure frequency per 28 days of each seizure type identified at the time of screening or baseline during the maintenance period and full treatment period (52 weeks).
- Treatment response as defined by ≥50% reduction in convulsive (DS) and MMD (LGS) seizure frequency per 28 days from baseline every12 weeks after the initial 12 weeks of the maintenance period.
- Treatment response as defined by ≥50% reduction in convulsive (DS) and MMD (LGS) seizure frequency per 28 days from baseline during the initial 16 weeks of the full treatment period (4 weeks of titration period + initial 12 weeks of maintenance period).
- Clinical Global Impression of Improvement (CGI-I) (clinician).
- Caregiver Global Impression of Improvement (Care GI-I).
- CGI-I Seizure Intensity and Duration.
- CGI-I Nonseizure Symptoms completed by clinician with input from the caregivers.
- Quality of Life Inventory-Disability (QI-Disability).
- Change in EQ-5D 5-level version (EQ-5D-5L) and EQ-5D visual analogue scale (EQ VAS) scores.
- Caregiver satisfaction questionnaire.
- Days when rescue ASM is used.
- The safety endpoints include
  - Incidence of TEAEs.
  - Columbia-Suicide Severity Rating Scale (C-SSRS).

– Ophthalmological evaluations.

4.0 STUDY DESIGN

4.1 Overall Design

This is a phase 3, open-label, nonrandomized, single-arm study in participants with DS or LGS who have been exposed to fenfluramine.

"Exposure" is defined as participants who are current or prior users of fenfluramine.

Note: Participants who have discontinued fenfluramine for reasons of lack of efficacy or intolerability are eligible as prior users.

Approximately 15 participants with DS and 30 participants with LGS will be enrolled in the study.

The study will consist of the following periods:

- A 4- to 6-week screening/baseline period.
- Approximately 52-week full treatment period including:
  - A 4-week titration period.
  - Approximately 48-week maintenance period.
- A taper period (up to 1 week) and follow-up period (1 week after the taper period concludes); this will not be required for participants enrolling in the extension study (ENDYMION 2).
- Follow-up visit/call occurs approximately 1 week after the taper period concludes.

This is an open-label study to receive standard-of-care plus soticlestat in participants who have been exposed to fenfluramine. Soticlestat added to current antiseizure therapy will be administered orally BID with or without food (oral or enteral feeds including but not limited to nasogastric tube [NG-tube] or via gastrostomy tube [G-tube] or low-profile gastric tube (Mic-Key Button), or a jejunostomy tube [J-tube]). See Section 6.2.6.2 for more details about study drug administration.

The total daily dose of study drug (soticlestat) will be calculated on the basis of body weight at Visit 1 (screening visit) and given BID. The dosing schedules by weight are shown in Table 4.a. The minimum dose allowed during the study is 100 mg BID (or 100 mg BID equivalent weight-based dosing for weight <45 kg). Participants who cannot tolerate the minimal dose will be discontinued from the study. Participants weighing <45 kg will be dispensed 20 mg mini-tablets. Participants weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets.

Intermediate doses between dose levels may be allowed after discussing with the medical monitor.

Table 4.a Dosing Schedules by Weight

	Dose 1 (Days 1-7): Adult Reference 100 mg BID		Dose 2 (Days 8-14): Adult Reference 200 mg BID		Dose 3 (Days 15-28): Adult Reference 300 mg BID	
	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini- tablets
10 to <15 kg Weight Reference Dose						
Soticlestat	40 mg BID	2 mini-tablets soticlestat BID	60 mg BID	3 mini-tablets soticlestat BID	100 mg BID	5 mini-tablets soticlestat BID
15 to <30 kg Weight Reference Dose						
Soticlestat	60 mg BID	3 mini-tablets soticlestat BID	120 mg BID	6 mini-tablets soticlestat BID	200 mg BID	10 mini-tablets soticlestat BID
30 to <45 kg Weight Reference Dose						
Soticlestat	80 mg BID	4 mini-tablets soticlestat BID	140 mg BID	7 mini-tablets soticlestat BID	200 mg BID	10 mini-tablets soticlestat BID
≥45 kg Weight Reference Dose						
Soticlestat	100 mg BID	1 tablet soticlestat BID OR 5 mini-tablets soticlestat BID	200 mg BID	2 tablets soticlestat BID OR 10 mini-tablets soticlestat BID	300 mg BID	3 tablets soticlestat BID OR 15 mini-tablets soticlestat BID

BID: twice daily.

Participants <45 kg may request adult size tabs for Dose 3 only.

The dose can be adjusted according to the participant's weight change after completing the initial 12 weeks of the maintenance period, per investigator judgement.

ASMs taken as SOC, should remain stable for initial 12 weeks of the maintenance period, after which, doses can be adjusted based on SOC and investigator judgement.

Rescue medication dose can be adjusted throughout the study as per SOC.

Soticlestat doses should also remain stable for initial 12 weeks of maintenance period, after which it can be adjusted according to participant weight changes and investigator judgement.

The study design allows virtual visits to be conducted via phone or an appropriate platform(s) as long as approved and aligned with institutional or local guidelines. The decision to perform a visit virtually is at the discretion of the investigator.

Screening (Visit 1), Visit 7 and final visit/early termination (ET) must be conducted in clinic or in person (home visits). Safety calls may be conducted virtually.

All other visits can be virtual (visits including assessment of Clinical Global Impression [CGI] scale[s] should be conducted via video call, not phone call), at investigator discretion and if permitted by local regulations. Additionally, home health visits may be conducted by site staff at the discretion of the investigator and if permitted by local regulations. During home visits,

assessment of CGI scale(s) should be conducted via video call and not phone call (if qualified rater is not present in person during home visit).

In addition, any visit identified as virtual in this protocol may be conducted in clinic and in person if requested by the participant/parent or guardian and/or at the investigator's discretion.

4.1.1 Dose Titration Period (4 Weeks)

Participants will take the initial dose of study drug, that is, Dose 1 (100 mg BID adult reference dose, weight-based dosing for weight <45 kg) the morning after the enrollment day (Day -1). Participants receiving the study drug at home through a courier should take it the morning after they receive it.

Approximately 7 days after starting Dose 1, study drug dose will be increased to Dose 2 (200 mg BID adult reference dose, weight-based dosing for weight <45 kg) and continued for approximately 7 days. Seven days after receiving Dose 2, the drug dose can be increased to, Dose 3 (300 mg BID adult reference dose, weight-based dosing for weight <45 kg). If the participants do not experience any tolerability issues, they will continue Dose 3 for the remainder of the titration period.

Participants will only be allowed to increase their dose within the 4-week 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. Intermediate doses between scheduled dose levels may be allowed after discussing with the medical monitor.

Participants who cannot tolerate the minimum dose of 100 mg BID (or weight-based equivalent dosing for participants weighing <45 kg) will be discontinued from the study. The maximum allowed dose is 300 mg BID (or weight-based equivalent dosing for participants weighing <45 kg).

The participants/parents or caregivers will be contacted by phone within approximately 2 days following each dose escalation to assess safety and tolerability of the study drug and again at the end of the titration period for that dose. The final dose tolerated by the end of the 4-week titration period should be maintained during the initial 12 weeks of the maintenance period unless tolerability issues arise.

Any changes to the dose levels provided in Table 4.a may be allowed after further discussion with medical monitor.

4.1.2 Maintenance Period (Approximately 48 Weeks)

In the absence of safety or tolerability considerations, the final dose level at the end of the titration period should be maintained for first 12 weeks of the maintenance period. The dose can be adjusted according to the participant's weight change after completing the initial 12 weeks of the maintenance period. 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 (300 mg BID adult reference dose, weight-based dosing for weight <45 kg) may be reduced to Dose 2 (200 mg BID adult reference dose, weight-based dosing for weight <45 kg), and Dose 2 may be

reduced to Dose 1 (100 mg BID adult reference dose, weight-based dosing for weight <45 kg). The minimum dose is Dose 1; participants who cannot tolerate the minimum dose will be discontinued from the study. The dose may be decreased during the initial 12 weeks maintenance period for safety or tolerability reasons as assessed by the investigator; however, if possible, dose changes should be discussed with the sponsor/designee. After the initial 12 weeks of maintenance period, intermediate doses between dose levels may be allowed after discussion with the medical monitor.

4.1.3 Study Discontinuation/Completion

At the end of overall maintenance period, at Visit 10, participants will have the option to enroll into the OLE study ENDYMION 2 on the dose they are receiving in the maintenance period in TAK-935-3004, as deemed appropriate by the investigator.

Participants not entering ENDYMION 2, will begin a 1-week taper period (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. On completion of the taper period a safety phone call or visit will be completed approximately 2 weeks after the participant's final visit/ET.

Participants who terminate the study early for reasons other than safety/tolerability may also have the opportunity to join ENDYMION 2 study at sponsor discretion.

4.1.4 Period of Evaluation

Approximately 60 weeks (including up to 6-week screening/baseline period, 52-week treatment period [4-week titration and 48-week maintenance periods], 1-week taper period for those discontinuing study drug, followed by a safety follow-up visit/call 1 week after the taper period ends.

For a schematic of the study design, see Section 1.2. For the Schedule of Activities (SoA), see Section 1.3.

4.2 Scientific Rationale for Study Design

DS and LGS are rare and severe forms of epilepsies that begin in early childhood. These are lifelong conditions that lead to significant neurological and developmental problems including severe cognitive disabilities and can also increase the risk of sudden unexpected death in epilepsy. Although there are over 30 ASMs used to treat seizures in this patient population in the clinical settings, approximately 40% of these patients continue to have treatment refractory seizures and will comprise the target patient population for this study.

This study is designed to obtain additional clinical efficacy and safety data of soticlestat in participants who have been exposed to fenfluramine.

Fenfluramine is approved for the treatment of DS and LGS by the Food and Drug Administration (FDA) and has recently received a marketing authorization in the EU for DS and LGS. The real-world data regarding its efficacy is limited due to the recent approval and few participants

with prior or concomitant use of fenfluramine are expected to be enrolled in the ongoing phase 3 studies of soticlestat.

This study will provide additional safety and effectiveness data of soticlestat as an add-on therapy in participants previously or currently exposed to fenfluramine. This study will be enrolling participants in countries where fenfluramine is recently approved for the treatment of seizures in DS and LGS.

Additional aims are to explore efficacy as assessed by the investigator (characterized by CGI-I) as well as by the caregivers, CGI-I in nonseizure-related symptoms, impact on quality of life, and the safety, tolerability, of soticlestat administration in pediatric and adult participants with DS and LGS.

4.2.1 Participant Input Into Design

Not applicable as participants/caregiver input was not required in this study design.

4.3 Justification for Dose

Dose selection is based on a comprehensive analysis of the safety, tolerability, PK, and PD data from 4 completed single- and multiple-dose phase 1 studies in healthy participants; the safety, tolerability, and PK data from the phase 1b/2a study of soticlestat as adjunctive therapy in adult participants with DEEs; and the efficacy, safety, PK, and PD data in the ELEKTRA study in pediatric participants 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 participants with DS while maintaining a favorable safety and tolerability profile. A numerical reduction in seizure frequency was also noted in participants with LGS. 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 (Nishi et al. 2020). A 75% reduction in the severity score was associated with a 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 cholesterol 24-hydroxylase [CH24H] inhibitor, soticlestat, with liquid chromatography/tandem mass spectrometry. Report number: 16354). In summary, these nonclinical pharmacology studies suggest that a 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 target occupancy and 24HC reduction required for efficacy. On the basis of a population PK/PD/EO model using data from 4 phase 1 studies in healthy participants, the phase 1b/2a study in adult participants with DEEs, and the ELEKTRA study in pediatric participants 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 <60 kg) was administered in ELEKTRA, and demonstrated a seizure reduction in participants with LGS while maintaining a favorable safety and tolerability profile. Approximately 79% of participants 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 participants with LGS reported a 20.6% median reduction in drop seizures, while those participants 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 participants 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 participants (80.3%) experiencing at least 1 TEAE compared with 52 placebo participants (74.3%). The most frequent TEAEs reported in soticlestat-treated participants with ≥5% difference from placebo were lethargy and constipation. The incidence of SAEs was similar in both soticlestat and placebo groups, with 11 participants (15.5%) in the soticlestat group experiencing at least 1 treatment-emergent SAE compared with 13 participants (18.6%) in the placebo group. There were no deaths reported. The combination of drop 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 <45 kg BID). Before reaching the target dose in the current study, participants will receive the minimum soticlestat dose (ie, 100 mg BID adult equivalent dose for 1 week, followed by 200 mg BID adult equivalent dose for 1 week) in the titration phase. The goal of titration is to reach the target final dose of 300 mg BID adult equivalent dose after a 14-day titration period; the same titration regimen was evaluated in study ELEKTRA and demonstrated a favorable safety and tolerability profile in addition to drop seizure reduction as above.

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 participants at or above the reference value was set to 35%. Setting the percentage threshold at “35%” ensures the safety of pediatric participants because 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 4.a.

4.4 Overall End of Study

The global end-of-the-study is defined as the last scheduled procedure for the last participant in the study.

5.0 STUDY POPULATION

Informed consent must be obtained before any screening procedures other than activities the institutional review board (IRB)/independent ethics committee (IEC) has specifically approved for use as prescreening procedures. Specifically, informed consent must be obtained before beginning test procedures outlined in the SoA (Section 1.3). Informed consent requirements are described in Section 10.1.3.

All entry criteria, including test results, must be confirmed by the investigator before enrollment. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Investigators must account for all individuals who sign informed consent forms (ICFs), regardless of the outcome of the screening, by completing the required electronic case report forms (eCRFs).

Rescreening may be allowed after discussion with the medical monitor.

5.1 Inclusion Criteria

Participants must meet *all* of the following criteria to be eligible for inclusion in the study:

1. In the opinion of the investigator, the participant or the participant's parent or legal guardian or caregiver is capable of understanding and complying with protocol requirements, complete appropriate assessments, maintain an accurate and complete daily seizure diary and take study drug for the duration of the study.

   If the participant is living in a residential facility, a minimally possible number of staff member(s) at the facility who are the participant's primary caretaker(s) may be identified as caregivers who (per investigator's judgement) are capable of complying with protocol requirements as indicated above.
2. The participant/participant's legally acceptable representative has provided informed consent (that is, in writing, documented via a signed and dated ICF) and any required privacy authorization before the initiation of any study procedures.
3. The participant, of any sex, and aged ≥2 years, at the time of informed consent.
4. The participant has a documented clinical diagnosis of DS supported by variable combinations of typical clinical features such as those noted as follows and as determined by the investigator.
   - Onset of seizures usually in the first year of life.
   - History of fever-induced prolonged seizure as determined by the investigator

- May include prolonged (approximately 15 minutes or longer) hemi-clonic seizures.
- Multiple seizure types, which may include:
  - Generalized tonic-clonic.
  - Focal to bilateral tonic-clonic.
  - Clonic.
  - Myoclonic
- History of developmental delay/intellectual disability presenting after onset of seizures and usually presenting after 12 months of age.
- Documented genetic mutation consistent with DS is not required, but results of genetic testing will be collected if available. If genetic testing was not performed previously or if the *SCN1A* result is negative (without any other positive gene reported that is consistent clinically with DS), testing for *SCN1A* will be offered at the time of screening, per local restrictions.

OR

The participant has a documented clinical diagnosis of LGS supported by variable combinations of typical clinical features such as those noted as follows and as determined by the investigator.

- Onset of seizures usually between the ages of 1 and 8 years.
- Presence of multiple seizure types: including drop seizures (eg, tonic-atonic seizures) and other seizure types including atypical absence seizures, tonic-clonic, myoclonic, and partial seizures.
- History of abnormal EEG results (eg, slow spike and wave [<2.5 Hz], slow or disorganized EEG background, generalized paroxysmal fast activity).
- Developmental delay or intellectual disability consistent with LGS.

5. The participant has experienced failure of treatment to control seizures despite appropriate trials of at least 1 ASM based on historical information and is currently on an antiseizure therapy (eg, ASMs, vagus nerve stimulation [VNS], ketogenic/modified Atkins diet) or other treatment options considered as SOC.
6. The participant has been exposed to fenfluramine (currently on or used previously).

   Note: Participants, who have discontinued fenfluramine for reasons of lack of efficacy or intolerability are eligible as prior users.
7. The participant has a clinical diagnosis of LGS and a history of, on average, ≥12 MMD seizures in the last 90 days immediately before screening based on historical information, and the participant has ≥4 MMD seizures during a minimum of 4 weeks of seizure data collection during the prospective baseline period.

The total number of seizures includes only primary outcome seizure types with documentation as determined by the investigator:

- Hemi-clonic or focal clonic.
- Focal to bilateral tonic-clonic.
- Generalized tonic-clonic.
- Bilateral clonic.
- Convulsive status.
- Focal 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.

OR

The participant has a clinical diagnosis of DS and a history of, on average, ≥9 convulsive seizures in the last 90 days before screening visit based on the historical information, and the participant has ≥3 convulsive seizures during a minimum of 4 weeks of seizure data collection during the prospective baseline period.

The total number of seizures includes only primary outcome seizure types with documentation as determined by the investigator:

- Hemi-clonic or focal clonic.
- Focal to bilateral tonic-clonic.
- Generalized tonic-clonic.
- Bilateral clonic.
- Convulsive status.

8. The participant weighs ≥10 kg at the screening visit (Visit 1).
9. Artisanal cannabidiols/nonpharmaceutical grade cannabidiols are allowed. Participants should be on a stable dose for at least 4 weeks before the screening visit (Visit 1); the dosing regimen and manufacturer should remain constant during the initial 16 weeks of treatment period (including 4 weeks of titration period and 12 weeks of maintenance period) of the study. (Artisanal cannabidiols will not be counted as ASMs.)
10. The participant is currently taking 0 to 5 antiseizure treatments (eg. VNS, ketogenic diet) at stable doses, of which;
    a) Four can be ASMs, before the screening visit (Visit 1); benzodiazepines used chronically (daily) to treat seizures are considered ASMs. Cannabidiol (Epidiolex) is allowed where

available and should be counted as an ASM. ASM dosing regimen must remain constant during the initial 16 weeks of treatment period (4 weeks of titration + initial 12 weeks of maintenance).

b) If using a VNS, the participant must have had VNS placed at least 3 months before the screening visit (Visit 1) with stable settings for at least 4 weeks before the screening visit (Visit 1); VNS parameters must remain constant during the initial 16 weeks of treatment period (4 weeks of titration + initial 12 weeks of maintenance) of the study.

c) If on a ketogenic diet (or any other diet used for treatment of epilepsy, such as modified Atkins diet), the participant must have started the diet at least 3 months before the screening visit (Visit 1), and the participant's diet should be stable for 4 weeks before the screening visit (Visit 1); the participant should continue this diet during the initial 16 weeks of treatment period (4 weeks of titration + initial 12 weeks of maintenance) period of the study.

11. The use of felbamate is allowed provided that the participant does not meet the liver function test (LFT) exclusion criteria, the dose has been stable for at least 6 months before the screening (Visit 1), and the participant has had stable liver function (as determined by serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels) and hematology laboratory tests during the course of treatment.
12. Participants 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.

    *Definitions, effective and highly effective methods of contraception are described in Section 10.4.

5.1.1 Justification of Inclusion Criteria

All clinical studies in soticlestat are conducted or being conducted for participants aged at least 2 years. We do not have data in children younger than 2 years; furthermore, there is no appropriate formulation for participants younger than 2 years (ie, dose <20 mg) because it is currently under development. The appropriate dose for this age group is still under evaluation.

5.2 Exclusion Criteria

The participant will be excluded from the study if any of the following exclusion criteria are met:

1. The participant is an investigator site personnel directly affiliated with this study and/or their immediate family.

   Note: Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
2. The participant is a Takeda employee or immediate family member.

3. The participant is currently enrolled in a clinical study involving an investigational product or treatment device (ie, not approved in that country, other than soticlestat), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

   Note: Compatibility will be determined on the basis of consultation with the sponsor/designee.

4. The participant has participated in a clinical study involving another study drug in the last 30 days (or 5 half-lives of the study drug, whichever is longer) before screening (Visit 1).
5. The participant has a known hypersensitivity to any component of the soticlestat formulation.
6. The participant has an 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 sponsor/designee may be warranted.
7. The participant has any history of alcohol, opioid, or other drug use disorder, per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, within 2 years of the screening visit (Visit 1).
8. The participant is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the participant has attempted suicide within 12 months before the screening visit (Visit 1). Participants aged ≥6 years who have positive answers on item numbers 4 or 5 on the C-SSRS before dosing (Visit 2) are excluded. This scale will only be administered to participants aged ≥6 years at the time of enrollment or participants who turn 6 after enrollment.
9. The participant is unable to withhold the use of strong inducers of cytochrome P450 (CYP 3A4) during the entire clinical study, (except for ASMs [eg, carbamazepine, phenobarbital, phenytoin] and topical preparations).
10. The participant is currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no dietary restrictions for this study.

5.3.2 Contraception and Breastfeeding

5.3.2.1 Contraception for Participants Capable of Producing Viable Ova and/or Becoming Pregnant

Participants who are of childbearing potential (that is, capable of producing viable ova and/or becoming pregnant) must use effective (not applicable for Germany) or highly effective contraception as agreed to in Inclusion Criterion 12. Section 10.4 defines childbearing potential and lists acceptable methods of contraception.

5.3.2.2 Contraception for Participants Capable of Producing Viable Sperm

Male participants 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.

5.4 Screening

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Diagnosis will be reviewed (medical history, seizure history, and other diagnostic procedures) by the investigator.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

5.4.1 Screen Failures

An individual who has provided informed consent to participate in the study may be categorized as a screen failure for any of the following reasons:

- Did not meet entrance criteria.
- AE.
- Lost to follow-up.
- Pregnancy.
- Withdrawal by participant/parent or legal guardian.
- Study terminated by sponsor.
- Other (specify).

Participants are **not** considered screen failures if they were enrolled but not treated. See Section 7.2.

Information about screen failures should be collected via the eCRFs, including participant identification, screening disposition (including the reason for screen failure), demography, inclusion/exclusion criteria, and AEs (if applicable). If a potential participant experiences an SAE during screening, all of the participant's screening eCRFs must be available for collection.

Participant identification numbers assigned to participants who do not meet eligibility criteria should not be reused.

An individual who has been designated a screen failure may be rescreened with a new participant ID, after discussion with the medical monitor.

5.5 Criteria for Temporarily Delaying Enrollment/Administration of Study Drug

Not applicable.

5.6 Enrollment

A participant is defined as enrolled when all of the following have occurred:

- The participant and/or the participant's legally acceptable representative has provided informed consent (that is, in writing, documented via a signed and dated ICF).
- The participant has provided assent to participate in the study, if applicable.
- The participant has completed screening, having satisfied all entry criteria.

6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Study Intervention(s) Administered

In this study, the interventions include:

- Investigational product: soticlestat
- Other products required for the study: not applicable

The table following describes the drug administered in this study.

Table 6.a Study Interventions Administered

Intervention Label	Soticlestat
Intervention Name	Soticlestat
Former Name(s) or Alias(es)	TAK-935
Intervention Description	Soticlestat in this study is administered BID as 20 mg mini-tablets or 100 mg tablets (dose calculated based on body weight).
Excipients	Mannitol (E 421) – 100 mg tablets only
Type	Drug
Dose Formulation	Mini-tablets and tablets
Unit Dose Strength(s)	20 mg mini-tablets or 100 mg tablets
Dosage Level(s)	BID at dose level as indicated in Section 4.1
Route of Administration	Orally with or without food (oral or enteral feeds including but not limited to NG-tube or via G-tube or Mic-Key Button, or a J-tube).
Use	Experimental
Classification	IMP
Authorization Status	Not authorized
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; J-tube: jejunostomy tube; NG-tube: nasogastric tube.

6.2 Preparation, Handling, Storage, and Accountability

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

Clinical study materials will be labeled according to the country's regulatory requirements. All participants will continue on SOC antiseizure therapies throughout the study (not provided by the sponsor).

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.

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.

6.2.1 Accountability Throughout the Study

The investigator or designee must ensure that the sponsor-supplied study product is used in accordance with the protocol and is only used for participants enrolled in the study.

To document appropriate use of sponsor-supplied study product (Section 6.1), the investigator or designee must maintain 100% accountability for all sponsor-supplied study drugs that the site receives and dispenses during his or her entire participation in the study.

Proper drug accountability includes, but is not limited to:

- The investigator or designee must maintain records of all sponsor-supplied study drugs delivery to the site, current site inventory, dispensing for use by each participant, and return to the sponsor or designee.
- The investigator or designee must record this inventory on a sponsor-approved drug accountability log.
- Based on entries in the log, it must be possible to reconcile study products delivered with those used and returned.
- All study products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.
- All study drugs not returned to the site by a participant must be investigated by the site and appropriately documented on the log.
- 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 participant to whom sponsor-supplied drug is dispensed.

6.2.2 Receiving Product at the Site

Investigators will be provided with sufficient amounts of the study drug to carry out this protocol for the agreed number of participants.

On receipt of sponsor-supplied study drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition.

This may include an examination of temperature-monitoring devices.

If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment in the IRT. If there are any discrepancies between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

6.2.3 Handling and Storage at the Site

The investigator bears the overall responsibility for ensuring that the study drugs are stored in an appropriate location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

An appropriate storage location is one that is secure, with access that is limited to the investigator and authorized site staff; and that is environmentally controlled (manually or automated) in accordance with labeled storage requirements.

The investigator is responsible for ensuring that soticlestat is maintained according to the requirements described in Table 6.b.

The investigator is responsible for ensuring that the investigational drug is maintained within an established temperature range, that the temperature is monitored throughout the duration of the study, and that records are maintained.

A daily temperature log of the drug storage area must be maintained every working day.

The temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified minimum/maximum thermometer) would require manual resetting on each recording.

The sponsor must be notified immediately on discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the impact of reported excursions in relation to the suitability of the product for future use and will inform the site of the decision accordingly. Under no circumstances should the product be dispensed to participants until the impact has been determined and the product is deemed appropriate for use by the sponsor.

Study drugs must be kept in these conditions until they are used or returned to the sponsor for destruction.

The sponsor should be notified immediately if there are any changes to the storage area of the study drug that could affect the integrity of the product(s), eg, fumigation of a storage room.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, the sponsor or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

Table 6.b Study Intervention(s): Storage Conditions

Intervention Label	Soticlestat
Intervention Name	Soticlestat
Required Environmental Storage Conditions	This product should be stored according to the labeled storage conditions and pharmacy manual

6.2.4 Labeling

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 drug 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.

6.2.5 Preparation

Refer to the pharmacy manual for any additional study drug preparation instructions, as required.

6.2.6 Dispensing/Administration

The investigator has overall responsibility for dispensing/administering the study drug.

Where permissible, tasks may be delegated to a qualified designee (for example, a pharmacist or a home healthcare representative) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or their designee will dispense the study drug only to participants enrolled in this study, following the procedures set out in the study protocol. Each participant will be given only the study drug carrying their treatment assignment.

All study drug provided to pediatric participants should be supervised by the study site/principal investigator and parent/legally authorized representative/caregiver, depending on the setting.

6.2.6.1 Dispensing

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 IRT.

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

6.2.6.2 Administration

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 4.a.

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

- Explaining the correct use of the study drug to the participant/parent or caregiver.
- Verifying that instructions are followed properly.
- Maintaining accurate records of study drug dispensing and collection.
- Returning or destroying 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 material 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. Clinical supply manager review and approval are required before proceeding.

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

All 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 a low-profile gastric tube (MIC-KEY Button). A J-tube may be considered following approval by the medical monitor or sponsor.

Note: Study drug will be administered only orally for participants 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 4.1.1 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 on the number of tablets/mini-tablets the participant is taking; a 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 is needed for each tablet taken.

For participants 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 participant/parent or caregiver. Other medications or enteral feeds should not be given concurrently with the study drug.

The scheduled dose can be administered or taken up to 4 hours after the scheduled time of dosing. If the participant/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. If a participant misses a dose, the missed dose should be skipped, and the participant should continue with his/her normal dosing schedule.

The planned daily dose and tablet count to be administered to participants during the titration period is shown in Section 4.1.1. During the titration period, 2 days after each dose escalation or taper, the participant/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.

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

6.2.7 Destruction or Return

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied product accountability and reconciliation before sponsor-supplied products are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied study drugs' accountability, return and/or destruction. Originals will be sent to the sponsor or designee.

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 participants enrolled in the study. The investigator or designee is responsible for ensuring that the study drug provided to the participant and returned from the participant 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 participant, 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.

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 participant 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/contract research organization (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.

Further instructions regarding the final disposition of unused study drugs are provided in the pharmacy manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

This is not a randomized study; therefore, no randomization schedule will be generated.

6.3.2 Blinding the Treatment Assignment

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

6.3.3 Unblinding

Not applicable.

6.4 Study Drug Compliance

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 participant or parent or caregiver and reviewed by the site personnel. The participant or parent or caregiver will be required to bring used/unused study drug and the daily seizure and medication diary to each site visit. All participants or parents or caregivers 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 participant's source records.

Compliance with study drug and seizure diary will be assessed at each visit (or unscheduled visits per principal investigator discretion).

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

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

6.5 Dose Modification

During the titration period, a decrease in dose level (to Dose 2 or Dose 1) is allowed if required for safety and tolerability. Doses between the scheduled dose levels may be allowed after discussing with the medical monitor.

Participants who cannot tolerate the minimum dose of 100 mg BID (or weight-based equivalent dosing <45 kg) will be discontinued from treatment. The maximum allowed dose is 300 mg BID. The final dose tolerated by the end of the 4-week titration period should be maintained until the end of the maintenance period, unless tolerability issues arise.

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); participants who cannot tolerate the minimum dose (Dose 1) will be discontinued from treatment. Dose decrease during the initial 12 weeks of the maintenance period are allowed as assessed by the investigator. Intermediate doses may be allowed after discussing with the medical monitor.

6.6 Continued Access to Study Drug After the End of the Study

Following completion of the study, participants will have the option to enroll in an OLE study, ENDYMION 2.

ENDYMION 2 is a multisite, phase 3, OLE study designed to obtain additional safety and tolerability data related to soticlestat administered long-term in participants who participated in either of the antecedent phase 3 clinical studies, TAK-935-3001 (participants with DS) or TAK-935-3002 (participants with LGS). Additional aims are to assess efficacy in terms of seizure frequency, non–seizure-related symptoms, impact on quality of life, and the PK and PD (concentration of 24HC) of soticlestat administration in pediatric and adult participants with DS or LGS.

Participants who will not enroll in ENDYMION 2, should be returned to the care of a physician and standard therapies initiated or resumed as required.

6.7 Treatment of Overdose

In this study, an overdose is defined as a known deliberate or accidental administration of the study drug, either to or by a study participant, at a dose above that assigned to that individual participant.

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

In addition, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study drug should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 1 day).

All cases of overdose, must be documented, including the quantity of the excess dose and the duration of the overdose. Because these events are not, in and of themselves, AEs, they should be reported regardless of whether any manifested signs or symptoms are considered AEs. If there are signs and symptoms meeting the criteria for reporting as AEs or SAEs, they should also be reported, as described in Section 10.3.

Overdose must be reported to the sponsor according to the SAE reporting procedure whether or not it resulted in an AE/SAE. However, the 24-hour reporting requirement for SAEs will not apply unless the event being reported also resulted in an SAE.

6.8 Concomitant Therapy

6.8.1 Rescue Medicine

The use of rescue medications is allowed throughout the study. The date of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded in the daily seizure and medication diary.

Rescue medication will not be supplied by the sponsor.

6.8.2 Excluded Medications

1. Strong CYP3A4 inducers are excluded from screening (Visit 1) until the end of the follow-up period, (except for ASMs [eg, carbamazepine, phenobarbital, phenytoin] and topical preparations) Appendix 1.
2. The use of herbal preparations (when used as an ASM) are not permitted.
3. Participants are instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

6.8.2.1 Justification of Excluded Medications

The above criteria were selected to avoid participant risk and potential interference with evaluation of endpoints.

Drug-drug interaction studies in healthy participants (ClinicalTrials.gov identifiers: NCT05064449 and NCT05098041) have shown that while soticlestat can be administered with CYP3A4 or UGT1A9 inhibitors without clinically meaningful drug-drug interactions, strong CYP3A inducers significantly reduce the concentration of soticlestat in plasma and are excluded in the currently ongoing clinical studies except for the ASMs (eg, carbamazepine, phenobarbital, phenytoin).

6.8.3 Permitted Concomitant Medications and Procedures

1. ASMs are allowed; benzodiazepines used chronically (daily) only to treat seizures are considered ASMs. Cannabidiol (Epidiolex) is allowed where available and should be counted as an ASM. SOC ASMs should be stable for at least 4 weeks before screening.
2. Vaccinations are allowed (including vaccination for COVID19); however, the sponsor/designee should be informed about changes in the participant's vaccination status and document it under the concomitant medication section of the eCRF.
3. The use of felbamate is allowed provided that the participant meets the relevant inclusion and exclusion criteria.
4. If the participant is using VNS, the device must have been placed at least 3 months before the screening visit with stable settings for >4 weeks; VNS parameters must remain constant during the initial 12 weeks of the maintenance period of the study (VNS will not be counted as an ASM).

All medications, including vitamin supplements and over-the-counter medications, will be documented throughout the study.

7.0 DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

This section describes the circumstances under which individual participants would withdraw or be discontinued from the study drug or from the study itself.

Section 10.1 describes circumstances in which specific sites or the study itself would be discontinued.

7.1 Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue study drug. If study drug is permanently discontinued, the participant may remain in the study to be evaluated for safety follow-up. See the SoA for data to be collected at the time of discontinuation of study drug (listed for ET), and follow-up and for any further evaluations that need to be completed (Section 1.3).

Potential circumstances for which a participant may permanently discontinue study drug or withdraw from study include:

1. Failure to meet continuation criteria: Enrollment in any other clinical study involving an investigational product or enrollment in any other type of clinical study judged not to be scientifically or medically compatible with this study.
2. Withdrawal by investigator: The investigator decides that the participant 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 participant/parent or legal guardian. Note: The specific reason for discontinuation should be recorded in the eCRF, therefore "withdrawal by participant/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 participant's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).
   c) The sponsor or its designee stops the clinical study at a particular site.

5. Discontinuation due to AE: The participant has experienced an AE that requires ET because continued participation imposes an unacceptable risk to the participant's health, or the participant is unwilling to continue because of the AE.

   If the investigator decides that the participant 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) LFT abnormalities: Study drug should be discontinued immediately (withdrawal of the participant from the study should be discussed with the sponsor/medical monitor) with appropriate clinical follow-up, including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status (see Section 10.6) if the following circumstances occur at any time during study drug treatment:

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

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

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

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

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

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

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

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

   Note: If the participant is found to be pregnant, the participant must be withdrawn immediately. The procedure is described in Section 10.4.3.

8. Coronavirus disease 2019 (COVID-19)/pandemic: If, in the opinion of the investigator, the safety of a study participant is at risk because the participant cannot complete key evaluations or adhere to critical mitigation steps, then the investigator should consider discontinuing that participant. In addition, for any such participant with COVID-19 diagnosis or in a pandemic circumstance, GCP for AE reporting processes will apply.

9. Death

10. Noncompliance with study drug.

11. Significant protocol deviation: The discovery after soticlestat dosing that the participant failed to meet protocol entry criteria or did not adhere to protocol requirements (after discussion with sponsor), and/or continued participation poses an unacceptable risk to the participant's health based on investigator judgement.

12. Lack of efficacy as determined by the investigator (withdrawal by participant/parent/legal-guardian should not be captured as lack of efficacy).

13. Other: The specific reason should be recorded in the eCRF.

Note: Participants who do not qualify for the study (screen failures) are not considered to have discontinued; instead see Section 5.4.1.

If the study drug is discontinued, regardless of the reason, the evaluations listed for ET visit will be performed as completely as possible.

The investigator must determine the reason(s) for discontinuation of study drug and/or the participant withdrawal from the study; date of discontinuation of the study drug and/or the participant withdrawal from the study; and the total amount of study drug administered and record this information in the eCRF.

7.1.1 Liver Chemistry Stopping Criteria

Participants with abnormal liver-associated test results should be evaluated to determine whether study drug should be continued, interrupted, or discontinued. See Section 10.6.

Discontinuation of study drug for abnormal liver test results is required by the investigator when a participant meets one of the conditions outlined in Section 10.3.5.1 or in the presence of abnormal liver chemistry results not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.2 Rechallenge

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2 Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of participant safety). The investigator is encouraged to discuss withdrawal of a participant with the medical monitor when possible.

The investigator may discontinue a participant's study participation at any time during the study when the participant meets the study termination criteria described in Section 7.1.

At the time of discontinuing from the study, if possible, an ET visit should be conducted, as shown in the SoA (Section 1.3). The primary criterion for termination must be recorded by the investigator. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. For any case of early discontinuation, the investigator should ask the participant to participate in the follow-up visit procedures, provided that the participant has not withdrawn consent for those procedures. If a participant refuses to complete ET and/or the follow-up procedures, this information will be recorded.

Participants who discontinue or withdraw will not be replaced.

7.3 Lost to Follow-up

A minimum of 3 documented attempts must be made to contact any participant (or their legally authorized representative) who is lost to follow-up at any time point before the last scheduled contact (in person or by phone or video). At least 1 of these documented attempts must include a written communication sent to the participant's last known address via courier or mail (with an acknowledgement of receipt request) asking that the participant be assessed for final safety evaluations and return any unused study drug.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Written informed consent must be obtained (signed and dated) before study assessments and procedures can be performed, as described in Section 10.1.3.

The following sections describe the study procedures and data to be collected at planned time points per the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Repeat or unscheduled samples may be taken for safety reasons or due to technical issues with the samples. Whenever possible, the same person should perform each assessment.

8.1 Demographics, Medical History, and Medication History

8.1.1 Demographics

Participant demographic information will be collected prior to the participant receiving the first dose of study drug.

Demographic information to be obtained will include:

- Age/date of birth (where permitted) at the time of informed consent.
- Sex.
- Race, ethnicity.
- Height and weight, of the participant at screening.

8.1.2 Medical History

Medical history, including concurrent medical conditions, will be collected.

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases relevant to the disease under study that resolved before the participant signed the ICF. Ongoing conditions are considered concurrent medical conditions.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant laboratory, physical examination, and/or vital signs abnormalities noted at screening examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

8.1.2.1 Historical Seizure Data

Per inclusion criteria, historical seizure information will be used to support study entry. It is very common for caregivers of participants with DS and LGS to maintain daily seizure diaries that capture both seizure type and frequency and days when no seizures occur as part of their SOC treatment regimen. A 3-month (90 days before screening) daily historical seizure diary will be reviewed at screening (Visit 1) to determine eligibility. In the event that daily seizure diaries are not routinely maintained as part of the SOC, the investigator will be asked to review in detail with the participants/caregiver the number of seizures over the last 3 months for each seizure type and attest eligibility to the study at screening (Visit 1).

8.1.3 Prior and Concomitant Treatments/Medications

Prior and concomitant treatments and medications will be collected and recorded in the participant's source document.

Such treatments/medications include but are not limited to:

- Medications or vaccines.
- Over-the-counter or prescription medicines.
- Recreational drugs.
- Vitamins.
- Herbal supplements.
- Medications relevant to the eligibility criteria.
- Other specific categories of interest.

Prior medications/treatments are defined as those that were:

- Stopped at or within 90 days before signing the ICF (note: all prior ASMs including fenfluramine use or its reason for discontinuation [if applicable] will be documented regardless of when it was stopped).

Concomitant medications/treatments are defined as those given in addition to the study drug:

- Between the signing of the ICF and participant completion.
- Between the first dose of study drug and the end of the follow-up period, inclusive.

- Starting before the signing of the ICF and continuing during the study.

Concomitant medications may be prescribed by a physician or obtained by the participant over the counter. Concomitant medication is not provided by the sponsor.

At each study visit, participants/parent or caregiver will be asked whether they have taken any medication or received any treatment 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.

Information to be recorded (including prior ASMs) will include:

- Identification of the medication or treatment.
- Reason for use.
- Dates of treatment/medication administration: start and end dates.
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.1.4 Diagnostic Criteria/Disease Classification

Refer to Inclusion Criterion 4 for diagnostic criteria of DS and LGS.

8.2 Efficacy Assessments

Efficacy measurements include:

- Seizure frequency captured via diaries.
- Clinician administered assessments.
- Observer-reported outcomes (as completed by the caregiver as applicable). These assessments are described in Section 8.4.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Investigators are responsible for monitoring the safety of participants 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 participant.

The investigator is responsible for the appropriate medical care of participants 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 participant to discontinue before completing the study. The participant should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

8.3.1 Physical Examinations

A baseline physical examination (defined as the assessment before first dose of study drug) will consist of the following body systems: eyes; ears; nose; throat; cardiovascular system; respiratory system; gastrointestinal system; dermatologic system; musculoskeletal system; extremities; nervous system; lymph nodes; and other (if required per principal investigator discretion).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

All subsequent physical examinations should assess clinically significant changes from the baseline physical examination. Physical examination information should be entered on the eCRFs as part of the medical history or in the context of AEs.

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 participant until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

8.3.2 Vital Signs

Vital signs will include:

- Temperature.
- Respiratory rate.
- Sitting blood pressure (systolic and diastolic, resting more than 5 minutes).
- Pulse (beats per minute).

Blood pressure should be determined by cuff (using the same method, the same arm, and the same position throughout the study). Manual techniques will be used only if an automated device is not available.

The investigator will assess whether a change in vital signs from baseline may be deemed clinically significant on the Vital Signs eCRF and whether the change should be considered and recorded as an AE on 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 participant until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

8.3.2.1 Weight and Height

Weight and height will be measured and recorded.

A participant should have weight and height measured while wearing indoor clothing and with shoes off. Weight is collected in kilograms (kg). Height is recorded in centimeters (cm).

If unable to obtain height or weight, data may be collected from other sources (eg, medical records or the participant's caregiver). The investigator must record in the source document the reason for not obtaining height or weight (eg, the participant is in a wheelchair).

8.3.3 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 participant's inability to cooperate, the reason should be documented. Partially completed neurological examinations may not be considered protocol deviations, as, in this patient population, complete neurological examination may be difficult to conduct.

8.3.4 Ophthalmological Evaluation Procedure

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

1. Age and developmentally appropriate quantitative visual acuity.
    a) If the participant 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 participants 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 conducted at baseline (between the screening and enrollment visits), at Day 112 (±2 weeks) and at Day 364 (±1 weeks) or at the ET visit for those participants who do not complete the study.

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

8.3.5 Clinical Safety Laboratory Tests

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the local laboratory requirements and regulations, laboratory manual, and the SoA (Section 1.3). Details about these procedures and required safety monitoring will be given in the laboratory manual if required.

The local laboratories will perform laboratory tests for hematology, serum chemistries, and urinalysis.

The clinical laboratory will return these results, along with their reference ranges, to the investigator. The investigator is responsible for reviewing the laboratory report, documenting this review, and filing the laboratory report with the source documents.

Abnormal laboratory findings associated with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

Clinically significant abnormal laboratory values obtained during participation in the study or within 4 weeks after the last dose of study drug should be repeated until the values return to normal or the baseline value or are no longer considered clinically significant by the investigator or medical monitor. The investigator should evaluate whether the laboratory result meets the AE criteria in Section 10.3.

For participants with treatment-emergent ALT elevations >3 × ULN, see Section 10.6 for additional monitoring, evaluation, and follow-up recommendations.

Abnormal clinical laboratory values that are unexpected or not explained by the participant's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

Investigators must document their review of each laboratory safety report.

The investigator must record the following types of laboratory test results on the laboratory eCRF and if applicable on the AE eCRF:

- Any changes that are considered clinically significant by the investigator (eg, SAE or AE or dose modification).
- Any laboratory test results (local laboratory, nonprotocol specific local laboratory) that are used to make a study drug decision, that require a change in participant management, or that are used to make a response evaluation.

8.3.6 Pregnancy Testing

A urine pregnancy test will be performed on all participants of childbearing potential at times described in the SoA (Section 1.3). For participants of childbearing potential, pregnancy test at

Visit 2 (Day -1/enrollment) is not required for eligibility if Visit 1 (screening) test is negative and if the investigator does not deem it necessary to repeat pregnancy test at Visit 2 (Day -1/enrollment). Additional pregnancy tests (serum or urine) may be performed throughout the study at the investigator's discretion.

If a participant becomes pregnant during the study, the participant will be immediately discontinued from study intervention, withdrawn from the study, and the pregnancy must be followed as described in Section 10.4.3.

8.3.7 Suicidal Ideation and Behavior Risk Monitoring

Suicidal ideation and behavior will be assessed in participants aged ≥6 years by use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, participant 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) (Posner et al. 2011).

Two versions of the C-SSRS will be used in this study for all participants ages ≥6 years: the C-SSRS Children's Screening/Baseline (recall period lifetime/12 months) and the C-SSRS Children's Since-Last-Visit. Children who are younger than 6 years at the start of the study will have an unscheduled visit after turning age 6 years, at which time the C-SSRS Children's Screening/Baseline version will be completed. The C-SSRS Children's Since-Last-Visit version will be completed at the end of the study.

Study staff trained in the administration of the C-SSRS will assess participant suicidality using the C-SSRS, eliciting answers from the participant/parent or caregiver. Participants aged ≥6 years who have positive answers on item numbers 4 or 5 on the C-SSRS before dosing (Visit 2) are excluded, see Exclusion Criterion 8. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator. If a participant exhibits signs of suicidal ideation or behavior, the participant will be withdrawn as described in Section 7.1.

8.3.8 AEs, SAEs, and Other Safety Reporting

The definitions of AEs and SAEs are provided in Section 10.3.

The investigator and any qualified designees are responsible for collecting, detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for follow-up of these events (see Section 10.3.4).

Any findings from investigator- or designee-administered assessments or patient reported outcomes assessments 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 these instruments, then proper follow-up with the participant for medical evaluation should be undertaken. If it is determined through this follow-up that an AE not previously reported has been identified, normal reporting requirements should be applied.

8.3.8.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until either the final visit (for participants enrolling into ENDYMION 2) or the final safety follow-up visit (for participants not enrolling into ENDYMION 2) at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately. Under no circumstance should this exceed 24 hours. The investigator will also submit any updated SAE data within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor via the reporting method described in Section 10.3.4.6.

8.3.8.2 Method of Detecting AEs and SAEs

At each study visit specified in the SoA, participant/participant's caregiver, or legally authorized representative will be questioned in a general way to ascertain if AEs have occurred since the previous visit. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences without introducing bias. Participants may report AEs occurring at any time during the study.

8.3.8.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All participants experiencing AEs, whether considered associated with the use of the study drug or not, will be documented in the AE page of the eCRF.

All AEs must be monitored until the end of the study or until the event resolves, stabilizes, is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

SAEs must be monitored until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Information to be documented for each event is defined in Section 10.3.4.

Further information on follow-up procedures is provided in Section 10.3.

8.3.8.4 Regulatory Reporting Requirements for SAEs

All SAEs must be recorded and reported to the sponsor or designee immediately, via the procedure described in Section 10.3.5. Under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met. The sponsor has a legal responsibility to notify both the

local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or state other documents and will notify the IRBs/IECs, if appropriate according to local requirements.

The sponsor or designee must prepare safety reports for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forward them to investigators as necessary.

8.3.8.4.1 Reporting of Abnormal Liver-Associated Test Results

If participants experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total and direct bilirubin, gamma-glutamyl transferase, 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 10.6 and Figure 10.a for the appropriate guidance on reporting abnormal LFTs.)

If a participant is noted to have elevated ALT or AST >3 × 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 participant details. and possible alternative etiologies. The abnormality should be recorded as a TEAE (please refer to Section 10.2.1).

If a participant is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, a case report form (CRF) must be completed and transmitted with the SAE Report form (per Section 10.2.2). The investigator must contact the medical monitor for discussion of the relevant participant 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 10.a must also be performed.

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

8.3.8.5 Pregnancy in a Participant or Participant's Partner During the Study

Details about all pregnancies in participants or their partners will be collected after the start of study drug and until 30 days after end of the study. Collection of pregnancy data from a participant's partner requires the partner's informed consent.

To the extent possible, the investigator will collect follow-up information on the outcome of the pregnancy and the neonate, and the information will be forwarded to the sponsor.

Once a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours.

Pregnancy itself is not considered to be an AE or SAE; however, AEs or SAEs associated with pregnancy must be reported as such, including:

- Any pregnancy complication or elective termination of a pregnancy for medical reasons (to be reported as an AE or SAE).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) (to be reported as SAEs).
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 10.3.4.7. Although the investigator is not obligated to actively seek poststudy pregnancy-related SAE information from former study participants or their partners, he or she may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study drug and withdrawn from the study immediately.

8.3.8.6 Deaths

Any death that occurs during the study will be reported per SAE reporting procedure, and should be carefully followed up to assess and identify the cause for death.

8.3.8.7 AESIs

An AESI (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 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.

Refer to Section 10.3.3.2 for list of events that will be reported as AESIs for this study.

AESIs must be recorded as AEs in the eCRF within 24 hours. An evaluation form along with all documentation must be submitted to the sponsor.

8.3.8.8 SSR

For EU countries only: abuse, misuse, overdose, medication error and other uses not foreseen in the protocol must be reported to sponsor within 7 days on a paper SSR 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.

8.4 Clinical Outcome Assessments

Clinical Outcome Assessment	Version Number	Reporter
CGI Baseline and Care GI Baseline	Adapted for patient population by sponsor for soticlestat development program	Clinician and caregiver (via Clinician)
CGI Baseline–Seizure Intensity and Duration	Adapted for patient population by sponsor for soticlestat development program	Clinician
CGI Baseline–Nonseizure Symptoms	Adapted for patient population by sponsor for soticlestat development program	Clinician
CGI-I	Adapted for patient population	Clinician
CGI-I Seizure Intensity and Duration	Adapted for patient population	Clinician
CGI-I Nonseizure Symptoms	Adapted for patient population	Clinician
Care GI-I	Created by sponsor for soticlestat development program	Caregiver (via clinician)
QI-Disability	2017	Caregiver
EQ-5D-5L	EQ-5D-5L 2009 EQ-5D 5-Level v1.1, self-complete	Caregiver (self-report about the caregiver's own quality of life)
Caregiver satisfaction questionnaire	Created by sponsor for soticlestat development program	Caregiver

8.4.1 CGI Baseline Questionnaires (Clinician)

For assessing baseline CGI of overall illness severity at baseline, the investigator or designee will complete 3 CGI Baseline questionnaires, 1 for overall baseline clinical impression, 1 for seizure intensity and duration, and another for nonseizure symptoms. The baseline questionnaires must be referenced during postbaseline CGI-I assessments to rate the change scores for CGI-I, CGI-I Seizure Intensity and Duration, and CGI-I Nonseizure Symptoms. The CGIs have been adapted from (Guy 1976) for this study population by the sponsor and will be provided by sponsor. These CGI Baseline questionnaires have been created as a reference document for the clinician's (and participant/parent/caregiver's) use and these data are not required to be entered into the electronic data capture or eCRF.

8.4.1.1 CGI Baseline and Care GI Baseline

For assessing baseline disease severity to inform subsequent CGI-I and Care GI-I ratings, the investigator or designee will complete the CGI Baseline/Care GI Baseline questionnaire. The investigator or designee will record their overall clinical impression of disease severity at

baseline. They will interview parent/caregiver and use input from parent/caregiver to inform their overall clinical impression assessment (Guy 1976).

For assessing Care GI Baseline of overall illness severity, investigator or designee will record on behalf of the parent/caregiver's assessment of the participant's overall condition using the same questionnaire. This questionnaire will be completed at the time point specified in Section 1.3.

8.4.1.2 CGI Baseline–Seizure Intensity and Duration

For assessing baseline CGI Seizure Intensity and Duration, the investigator or designee will complete the CGI Baseline–Seizure Intensity and Duration questionnaire. The investigator or designee will record an objective and comprehensive description of seizure frequency, intensity, and duration, based on input from the caregiver's report on the participant's functioning (Guy 1976).

8.4.1.3 CGI Baseline–Nonseizure Symptoms

For assessing baseline CGI Nonseizure Symptoms, the investigator or designee will complete the CGI Baseline–Non-Seizure Symptoms questionnaire. The investigator or designee will record how the participant is functioning in the past month for each of the following domains: communication, alertness, and disruptive behaviors (Guy 1976).

8.4.2 CGI-I (Clinician)

The CGI-I (clinician) is a 7-point Likert scale that the investigator uses to rate a participant's change (improvement) in overall seizure control, nonseizure symptoms, and behavior, as well as how well the participant is tolerating study drug and side effects, compared with baseline (before treatment with the study drug). The participant 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 time points specified in Section 1.3.

8.4.3 CGI-I Seizure Intensity and Duration (Clinician)

The CGI-I Seizure Intensity and Duration instrument is used by the investigator (with input from the parent/caregiver as needed) to rate changes in intensity and/or duration of the most impactful seizures compared with the baseline assessment. The participant'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 investigator or designee will complete the CGI-I Seizure Intensity and Duration in consultation with the primary caregiver at the time points specified in Section 1.3.

8.4.4 CGI-I Nonseizure Symptoms (Clinician)

The CGI-I Nonseizure Symptoms instrument is a series of single-item assessments that the investigator (with input from the parent/caregiver as needed) uses to rate improvement in the symptoms and impacts in select nonseizure domains (including communication, alertness, and

disruptive behaviors) since initiating the study drug at baseline. The participant 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 time points specified in Section 1.3.

8.4.5 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 (before treatment with the study drug). The participant 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 time points specified in Section 1.3.

8.4.6 QI-Disability (Parent/Caregiver Version)

The QI-Disability tool is a parent/caregiver-reported questionnaire that evaluates quality of life in children with intellectual disabilities (Downs et al. 2019). It contains 32 items covering 6 domains of quality of life: physical health (4 items), positive emotions (4 items), negative emotions (7 items), social interaction (7 items), leisure and the outdoors (5 items), and independence (5 items). Items are rated on a Likert scale of: Never, Rarely, Sometimes, Often and Very Often; the Negative Emotions domain items are reverse coded. Items are linearly transformed to a scale of 0 to 100, with higher scores representing better quality of life. Parents/caregivers report on their child's life over the past month.

The parent/caregiver-reported questionnaires will be administered according to the SoA (Section 1.3).

8.4.7 EQ-5D-5L Quality of Life Scale (Assessing Caregiver's Health)

The EQ-5D-5L is the 5–response level version of the EQ-5D instrument. The EQ-5D-5L is a preference-based measure of health status suitable for calculating quality-adjusted life years to inform economic evaluations. It consists of 2 sections, a descriptive system questionnaire and the EQ VAS. The questionnaire provides a descriptive profile across the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the EQ-5D-5L version, each dimension has 5 response levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The parents or caregivers are asked to indicate their own health quality of life by selecting the most appropriate statement in each of the dimensions. In addition, the EQ VAS is used to indicate the general health status by rating their health "today" from 0 (worst) to 100 (best health you can imagine). These questionnaires will be administered according to the SoA (Section 1.3).

8.5 Diaries

Seizure frequency will be collected daily via a seizure and medication paper diary. For participants meeting eligibility criteria the study site will provide paper diaries to caregivers/parents (or participants, if appropriate) to be completed daily between screening period and the last study visit.

Caregivers or participants (if applicable) will be instructed to record seizures or document seizure-free days in the diary daily (record within 7 days, if missed). Seizures should continue to be recorded even if treatment is discontinued.

All entries will be reviewed by the investigator with the participant/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 discussed with medical monitor, if needed.

These diaries may also capture additional information such as the following:

- Rescue medication/background ASM.
- Soticlestat dosing (during study).

At each visit and any other time point deemed to be appropriate by the investigator, the paper diary will be reviewed and collected.

The paper diary will be translated into the regional languages as required. Additional instructions on how to complete the paper diary will also be provided to the site and parent/caregiver.

8.6 Health Economics/Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

8.7 Genetics

Genetics will not be evaluated in this study.

8.8 Other

8.8.1 Caregiver Satisfaction Questionnaire

The caregiver satisfaction questionnaire is a 7-point Likert scale that the caregiver uses to rate overall satisfaction with soticlestat. The parent/caregiver is asked to consider the study participant's symptoms over the past 4 weeks and rate overall satisfaction with soticlestat using the following rating options: extremely satisfied, very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied, extremely dissatisfied.

The parent/caregiver will complete the caregiver satisfaction questionnaire according to the SoA (Section 1.3).

8.9 PK

PK parameters are not evaluated in this study.

8.10 PD

PD parameters are not evaluated in this study.

8.11 Biomarkers

Biomarkers will not be evaluated in this study.

8.11.1 Bioanalytical Methods

Not applicable.

9.0 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be prepared and finalized before database lock. The SAP will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all study objectives.

9.1 Statistical Hypotheses

No tests of statistical hypotheses are planned for any endpoints.

9.2 Analysis Sets

Safety analysis set: All participants who take at least 1 dose of study drug

Intent-to-treat (ITT) analysis set: All participants who enroll in the study.

Modified intent-to-treat (mITT) analysis set: All enrolled participants who take at least 1 dose of study drug and are assessed for seizures for at least 1 day in the treatment period.

9.3 Efficacy Analyses

Efficacy analyses will be performed using the mITT analysis set. Results will be presented separately for the DS and LGS cohorts using descriptive statistics. Analyses will be based on as-observed data. No imputation will be implemented.

For all efficacy analyses on seizure frequency, baseline refers to the prospective 4- to 6-week screening/baseline period. Baseline assessment for efficacy analyses other than seizure is the assessment before and closest to the first administration of the study drug unless otherwise specified.

9.3.1 Primary Efficacy Endpoint

Percent change from baseline in primary seizure frequency (convulsive for DS and MMD for LGS) per 28 days during the initial 12 weeks of the maintenance period will be summarized

using descriptive statistics including mean, median, SD, first quartile, third quartile, minimum, and maximum. A distribution-free 95% CI for the median will be presented.

9.3.2 Exploratory Efficacy Endpoints

Percent change from baseline in seizure frequency (convulsive for DS and MMD for LGS) per 28 days and total seizure frequency per 28 days will be summarized for the initial 16 weeks of the treatment period (4 weeks of titration + initial 12 weeks of maintenance), and every 12-week period thereafter.

Descriptive summaries of CGI-I, Care GI-I, CGI-I Seizure Intensity and Duration, CGI-I Nonseizure Symptoms, QI-Disability, caregiver satisfaction, and EQ-5D-5L will be presented for each scheduled collection time point and at end of study, as appropriate. 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. Other binary endpoints will be summarized in a similar fashion, as appropriate.

The EQ VAS score and the total score for QI-Disability will also be summarized in terms of change from baseline at each collection time point. EQ-5D-5L will be summarized descriptively by visit including baseline by presenting the number and percentage of responses in each level within each dimension.

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

Details will be provided in the SAP for appropriate summaries based on data type for the exploratory endpoints.

9.4 Safety Analyses

Safety analyses will be performed using the safety analysis set. Results will be presented descriptively. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be summarized using Preferred Terms and primary System Organ Classes.

Data summaries will be displayed for incidence of TEAEs, clinical laboratory variables, and vital sign parameters. Ophthalmological evaluations and C-SSRS will be listed by participant.

9.5 Multiplicity Adjustment

No adjustments for multiplicity are required.

9.6 Other Analyses

Demographic and other baseline characteristics will be summarized descriptively using the safety analysis set by DS and LGS cohorts. Medical history and medication history will be listed. All participants who discontinue from the study will be identified. If known, a reason for their

discontinuation will be given. Disposition information will be presented using the ITT analysis set.

9.7 Interim Analysis

Interim data cuts from this ongoing study will be analyzed to support any regulatory submissions. Since there is no hypothesis testing involved, no interim analysis will require spending any type-I error.

9.8 Determination of Sample Size

This study plans to enroll approximately 15 participants with DS and 30 participants with LGS. The study is not powered for hypothesis testing. The sample size is based on an estimation approach to ensure adequate precision to estimate the median change from baseline in convulsive (DS) or MMD (LGS) seizure frequency per 28 days during the first 12 weeks of the maintenance period. With the planned sample sizes, the expected half width of the 95% CI for the median is commensurate with the expected magnitude of the median.

With 15 participants in the DS cohort treated with soticlestat, the expected median percent change from baseline in convulsive seizure frequency during the first 12 weeks of the maintenance period is 35% and expected half width of the 95% CI is 30%.

With 30 participants in the LGS cohort, the expected median percent change from baseline in MMD seizure frequency during the first 12 weeks of the maintenance period is 37% and the expected half width of the 95% CI is 29%.

To determine the expected median and 95% CI half width, simulations were performed assuming the data follow a log normal distribution, and the distribution of underlying parameters (ie, mean and SD of the log transform of the data distribution) developed using results of the phase 2 ELEKTRA study.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted with the highest respect for the individual participants (ie, participants) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for GCP.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of study drug for shipment to the site.

10.1.2 Financial Disclosure

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s).

All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their site.

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

10.1.3 Informed Consent Process

10.1.3.1 Informed Consent Requirements in This Study

The goal of the informed consent process is to provide a potential participant or their legally authorized representative with sufficient information about the research to allow for an informed decision about their voluntary participation in the research study.

The informed consent process must facilitate the participant's comprehension of the information and allow adequate opportunity for the participant to ask questions and consider whether or not to participate. This process may extend beyond a participant's initial consent due to changing circumstances within the study, the therapeutic landscape, or the participant's situation.

When a participant and/or their authorized representative consents to participate in the study, their informed consent must be documented in writing via a signed and dated ICF. The date of the informed consent will also be collected in the eCRF along with the initial protocol version.

Minors or adults with intellectual disability comprise most of the participants with LGS or DS; therefore, the study would not be representative of these participant populations if it excluded them.

In this study, informed consent will be required from all participants and/or their legally authorized representatives.

A legally authorized representative is defined as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant, to the participant's participation in the procedure(s) involved in the study."

In this study, informed consent will be obtained using paper forms.

10.1.3.2 Standards the Informed Consent Follows

Informed consent documents, regardless of whether they are presented on paper or electronically, must 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 ICF:

- Explain the nature of the study, its objectives, potential risks and benefits.
- Describe the participant's rights and responsibilities, including what the study will require of the participant.
- Describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies, if applicable.
- State the fact the participant is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

More specifically, in seeking informed consent, the following information shall be provided to each participant:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the participant's participation.
- A description of the procedures to be followed, including invasive procedures.
- The identification of any procedures that are experimental.
- The estimated number of participants involved in the study.
- A description of the participant's responsibilities.
- A description of the conduct of the study.
- A statement describing the treatment(s) and the probability for random assignment to each treatment.
- A description of the possible side effects of the treatment that the participant may receive.
- A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.
- A description of any required restrictions related to contraception, pregnancy, and breastfeeding.
- Contraception requirements for participants of childbearing potential and for participants capable of making a partner pregnant.
- Definition of relevant terms, such as "childbearing potential."
- Statement that participants of childbearing potential will undergo regular pregnancy tests during the study.
- Explanation of required actions (such as discontinuation or treatment or from the study) if a participant or their partner becomes pregnant during study.

- Statement that the investigator will offer the participant the choice to receive unblinded treatment information if a pregnancy occurs.
- Statement that the participant must avoid breastfeeding during the study.
- A description of any benefits to the participant or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
- Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant and their important potential risks and benefits.
- A statement describing the extent to which confidentiality of records identifying the participant 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 an ICF, the participant or the participant's legally acceptable representative is authorizing such access.
- 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.
- The anticipated prorated payment(s), if any, to the participant for participating in the study.
- The anticipated expenses, if any, to the participant for participating in the study.
- An explanation of whom to contact for answers to pertinent questions about the research (investigator), participant's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the participant.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant otherwise is entitled
- A statement that the participant or the participant's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
- The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
- A statement that the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.
- A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
- The foreseeable circumstances or reasons under which the participant's participation in the study may be terminated.
- A participant authorization (either contained within the ICF or provided as a separate document) describing to the participant the contemplated and permissible uses and

disclosures of the participant's personal information (including personal health information) for purposes of conducting the study. The participant authorization must contain the following statements regarding the uses and disclosures of the participant's personal information:

- That deidentified 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.
- That is possible that de-identified personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer participants 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.
- That de-identified 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 participants, developing a better understanding of disease, and improving the efficiency of future clinical studies.
- That participants 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
- That the participant's identity will remain confidential in the event that study results are published.

- A statement that clinical study information from this study will be publicly disclosed in a publicly accessible website, such as clinicaltrials.gov.
- A description of the electronic devices and associated technology and its usage in the study.

10.1.3.3 Who Creates the Informed Consent Materials

The sponsor will provide sample ICFs to the investigator.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the participant authorization form.

The principal investigator will provide the sponsor with a copy of the ICF that was reviewed by the IRB/IEC and received their favorable opinion/approval. A copy of the IRB/IEC's written favorable opinion/approval of these documents must be provided to the sponsor before the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national

provisions) before study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/IEC requires modification of the sample documents that the sponsor provided, the documentation supporting this requirement must be provided to the sponsor. Both the IRB or IEC and the sponsor must approve the ICF participant authorization form (if applicable), and participant information sheet (if applicable) before use.

10.1.3.4 Who Conducts the Informed Consent Process

It is the responsibility of the investigator and the study personnel to:

- Explain the detailed elements of the ICF to the participant/participant's legally authorized representative.
- Answer all of the participant's/participant's legally authorized representative's questions about the study.
- Provide the participant/participant's legally authorized representative ample time to decide whether or not to participate in the study.
- Obtain written informed consent from all participants/participants' legally authorized representatives before any study-related procedures including screening assessments.

Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the participant is not capable of rendering adequate written informed consent, then the participant's legally acceptable representative may provide such consent for the participant in accordance with applicable laws and regulations.

If the participant, or the participant's legally acceptable representative, determines they will participate in the study, then they must sign and date the ICF and participant authorization form (if applicable) at the time of consent and before entering into the study.

The participant or the participant'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.

A copy of the informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative.

The investigator must also sign and date the ICF and participant authorization (if applicable) at the time of consent or after the receipt of participant signature (in the case of consent) and before the participant enters the study

Signed consent forms or certified copies of electronic signature must remain in each participant's study file at the site and must be available for verification at any time.

The investigator must document the date the participant signs the ICF in the participant's source documents.

10.1.3.5 Re-Consent

Participants/participants' legally authorized representatives are required to re-consent/re-assent if changes are made to the protocol or if new information is made available that may affect the willingness of current participants (those who are already enrolled and actively participating) to continue in the clinical investigation. Re-consent/assent should be obtained as described in Section 10.1.3.1.

Updated ICFs, individual consents, individual assents, individual re-consents and re-assents will be placed in the study master file. Re-consent information including the protocol version and re-consent date will also be recorded in the eCRFs.

10.1.4 Data Protection

The confidentiality of records that may be able to identify participants will be protected in accordance with applicable laws, regulations, and guidelines.

After participants have consented to take part in the study, the sponsor and/or its representatives reviews their source documents and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market soticlestat; national or local regulatory authorities; and the IRB/IEC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of participants' identities. Participants are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing participants' unique identifying number, relevant source documents, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.
- The participant must be informed that their source documents may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities

All United States (US)-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor.

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 preventative 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 the study participants, this would be done through the investigator.

10.1.4.1 Notice Regarding the Use and Transfer of the Investigator's Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and telephone number, and other personally identifiable information such as education and professional details, payment-related details (if applicable), identity information (eg, medical registration number) and information relating to his or her interactions and activities with or involving Takeda. 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 their licensing partners.
- Business partners assisting Takeda, its affiliates, and their 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.

In addition, where required by law or industry codes of practice, Takeda and/or its affiliates may have to report or publicly disclose any payments or transfers of value made in connection with the study by or on behalf of Takeda and/or its affiliates or their service providers to the investigator or their institution.

The legal basis on which Takeda and its affiliates will process the investigator's personal information for the above purposes are to comply with a legal obligation; or to perform any contract in place with the investigator (if applicable); or to meet the legitimate research, scientific and business interests of Takeda and its affiliates, including ensuring the proper performance of this study to the applicable standards, appropriate reporting of study results and archiving of study-related records and information, and further development and registration of the study drug or other compounds. The investigator may not be able to opt-out of this processing, or the investigator's choice to opt-out may impact his or her ability to continue to participate in this study and/or future studies involving Takeda and/or its affiliates.

Takeda and its affiliates will maintain physical, administrative and technical safeguards to protect the investigator's personal information from loss, misuse, unauthorized access, disclosure, alteration or destruction. 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.

However, where investigator's personal information is transferred to Takeda affiliates, licensing partners, business partners or service providers in such countries, Takeda will ensure that all adequate safeguards are in place and that all applicable laws and regulations are complied with in connection with such transfers.

The investigator's personal information will only be stored as long as necessary for the purposes for which it was collected participant to local laws and regulations and legitimate scientific, research and business needs.

Individuals located in the European Economic Area and in certain other countries have certain data participant rights which may be participant to limitations and/or restrictions. These rights include the right to: (i) request access to and rectification or erasure of their personal data; (ii) obtain restriction of processing or to object to processing of their personal data; (iii) the right to data portability; and (iv) obtain additional information regarding the safeguards Takeda has in place for cross-border transfers of their personal data. If the investigator wishes to exercise one of these rights, the investigator may use the contact information below.

Individuals located in the European Economic Area and in certain other countries may also have the right to lodge a complaint about the processing of their personal data with their local data protection authority.

The investigator can contact Takeda to exercise his or her rights, make inquiries or submit complaints concerning Takeda's processing of his or her personal information. Takeda will take

appropriate steps to address requests, inquiries and complaints. Takeda will respond to such requests within thirty (30) business days.

Contact Details:

Mailing Address: Attn: Data Protection Officer, Legal Department, Takeda Pharmaceuticals International AG, Thurgauerstrasse 130, CH-8152 Glattpark-Opfikon (Zurich), Switzerland.

Email Address: dataprivacy@takeda.com

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

10.1.5 Committees Structure

10.1.5.1 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.

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 ICF, and, if applicable, participant 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 participant 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, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation Until the site receives notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB/IEC. This may include notification to the IRBs/IECs regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by participants, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRBs/IECs, and submission of the investigator's final status report to IRBs/IECs. All

IRBs/IECs approvals and relevant documentation for these items must be provided to the sponsor or designee.

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRBs/IECs and sponsor.

10.1.6 Dissemination of Clinical Study Data

10.1.6.1 Study Results Disclosure

To ensure that information on clinical studies 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 studies before study start and disclose the results of those studies in a manner and timeframe compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on clinicaltrials.gov, other clinical trial registries/databases as required by law, and on Takeda's corporate website(s).

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in Case Report Form Completion Guidelines.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator per local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7.1 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. 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 sponsor will assess any protocol deviation. If it is likely to affect to a significant degree the safety and rights of a participant 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 site should document all protocol deviations in the participant'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 participant, or confound interpretation of primary study assessment.

10.1.7.2 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. The investigator and the study site head guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB/IEC.

Alternative approaches may be used to ensure data quality, data integrity, and participant safety (eg, remote source data review/source data verification via phone or video) as permitted by regional and local regulations. See the monitoring plan for additional details.

10.1.7.3 Audits

The study site also may be participant 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 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 guarantee access for quality assurance auditors to all study documents as described in Section 10.1.8.

10.1.8 Source Documents

All key data must be recorded in the participant'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: participant's medical file, appointment books, diaries, clinical outcome assessments, original clinical laboratory reports, histology reports, pathology reports, and x-rays. The investigator (as listed on the US FDA Form 1572) is responsible for maintaining adequate and accurate source documents.

The investigator must provide direct access to inspect facilities, including original source records relevant to this study (regardless of media), to: the sponsor or its authorized representatives; the respective national, local, or foreign regulatory authorities; the IRB/IEC; and auditors. These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, European Medicines Agency, United Kingdom Medicines and Healthcare products Regulatory Agency) or an auditor. The consent form includes a statement granting this access to source data.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.1.8.1 eCRFs

Completed eCRFs are required for each participant who has completed the consent process. 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.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

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 10.1.8) into the eCRF with guidance from eCRF Completion Guidelines.

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.

A study monitor from the sponsor or its designee will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Auditors, IRB/IEC members, or regulatory inspectors may also check the eCRF entries against the source documents.

Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

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 use of change and modification records of the eCRFs.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should also be included. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

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 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.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data. Alternative approaches may be used to ensure data quality, data integrity, and participant safety (eg, remote source data review via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

The CRFs should be approved by the investigator per study specifications and the sponsor's data delivery requirements.

The investigator's signature constitutes their attestation to the integrity of the data transmitted to the sponsor.

10.1.8.2 Documentation and Retention of Records

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. A definition of what constitutes source data and its origin can be found in for example, source data acknowledgment or monitoring guidelines.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous source documents or transfer records, depending on the study. Also, current source documents must be available.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8.3 Data Handling

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

Data are to be entered into a clinical database as specified in the CRO's data management plan or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

10.1.8.4 Record Retention

The investigator agrees to keep the records stipulated in Section 10.1.8.2 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, source documents, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs (including consent to use digital tools and applications, if applicable), participant authorization forms regarding the use of personal health information (if separate from the ICFs), query responses/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 participant's chart to ensure long term legibility. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (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(R2) Section 5.5.11 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.

10.1.9 Study and Site Start and Closure

10.1.9.1 First Act of Recruitment

The first act of recruitment is the first site open. For clinical study disclosure purposes, the study start date is the date when the first participant signed ICF.

10.1.9.2 Study/Site Termination

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. The sponsor reserves the right to close the study site at its sole discretion. Study sites will be closed on study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/IECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- For study termination:
  - Discontinuation of further study drug development.
- For site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

For sites in the EU, the sponsor will make an end of study declaration to the relevant competent authority as required by EU Clinical Trials Regulation (CTR) (Regulation No. 536/2014).

10.1.10 Publication Policy

During this study, until the open access period, only Takeda may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation.

Both during and after this study, all public disclosures containing data/information from this study must undergo ***review and receive written approval*** by the appropriate Takeda representative(s) ***before*** any public disclosure (including but not limited to submission,

presentation, posting on online platforms for archiving, and distribution of unpublished preprints).

This policy applies to all publication types, including: abstracts and presentations (oral and poster, including invited presentations) for scientific congresses; articles (original research manuscripts, review articles, invited articles), letters to the editor, and editorials, in scientific peer-reviewed journals; print, electronic and enhanced multimedia publications associated with traditional congress and journal publishing (such as, but not limited to, audio, visual/graphical or video abstracts or manuscript summaries; video or animated posters; augmented reality); books and book chapters.

Authorship will be determined in line with the requirements of the International Committee of Medical Journal Editors Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals, unless otherwise required by the journal or forum where the publication appears.

All publications must be developed with a dataset (such as statistical tables and listings, a clinical study report, and/or final report) that has been verified by a qualified Takeda employee per Takeda's internal standards. Data relevant to the development of Takeda publications must be shared with all authors via a secure site.

Publications derived from this study may never contain participants' direct identifiers (such as participant ID, initials) but may contain indirect/quasi identifiers (for example sex/gender, age/birth date, geographic indicators). Publications derived from this study may not include products' direct identifiers (lot numbers or batch numbers) unless specifically required by the journal or conference guidelines and if approved by Takeda.

Takeda requires the submission of all manuscripts resulting from this study, regardless of the intended audience or language, to journals that offer public availability via an Open Access platform.

The following types of information are required by ICH to be in the protocol if not addressed in another document (such as the site contracts):

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11 Responsibilities of the Sponsor and the Investigator

10.1.11.1 Sponsor Responsibilities

10.1.11.1.1 Study-Related Responsibilities

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

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

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

10.1.11.1.2 Insurance

Each participant in the study must be insured in accordance with the regulations applicable to the site where the participant 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 participants. Refer to the study site agreement regarding the sponsor's policy on participant compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee. The sponsor ensures that suitable clinical study insurance coverage is in place before the start of the study. An insurance certificate is supplied to the CRO as necessary.

10.1.11.2 Investigator Responsibilities

The investigator must perform the study in accordance with ICH GCP Guideline E6, EU CTR (Regulation No. 536/2014), other applicable regulatory requirements and guidelines, and rules considering the rights, safety, and wellbeing of human participants.

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:

- Conduct the study in accordance with the protocol.
- Personally conduct or supervise the staff who will assist in the protocol.

- If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
- Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential participants, before the receipt of written approval from relevant governing bodies/authorities.
- Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
- 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.
- 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 participants. 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.
- Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
- Obtain valid informed consent from each participant who participates in the study, and document the date of consent in the participant's medical chart. A valid ICF is the most current version approved by the IRB/IEC. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a participant authorization, then the investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.
- Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, and laboratory results, 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.
- Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
- Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
- Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

It is the investigator's responsibility to ensure that adequate time, appropriately trained personnel, and resources are available before commitment to participate in this study.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, on request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

If a potential research participant has a primary care physician, the investigator should, with the participant's consent, inform them of the participant's participation in the study.

The investigator listed on the Form FDA 1572 will verify by signature the integrity of the data transmitted to the sponsor.

The investigator will be responsible for reviewing data, reports, and interlaboratory/reader standardization methods (if applicable); facilitating monitoring and auditing activities.

10.1.11.2.1 Protocol Adherence and Investigator Agreement

The investigator and any subinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those participants who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRBs/IECs and provide them with a detailed written explanation. The investigator will also return all study drug, containers, and other study materials to the sponsor. On study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/IECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.1.11.2.2 Principal Investigator/Coordinating Investigator

The principal investigator/coordinating principal investigator will be required to review and sign the final clinical study report and by doing so agrees that it accurately describes the results of the study, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.1.12 Site Termination or Suspension

10.1.12.1 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 as otherwise permitted by the contractual agreement.

10.1.12.2 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 ET 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 risk/benefit is no longer acceptable for participants participating in the study.
- The soticlestat program Data Monitoring Committee recommends that the study should be suspended or terminated.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises participant safety.

10.1.12.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an IRB/IEC or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for ET 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.

10.2 Clinical Laboratory Tests

Table 10.a lists the tests that will be obtained for each laboratory specimen. These tests will be performed by the local laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10.a Protocol-Required Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet count Mean platelet volume Hemoglobin Hematocrit	RBC indices: MCV MCH %Reticulocytes		WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry [a]	Albumin BUN Creatinine	Potassium Sodium Calcium	AST ALT Alkaline phosphatase	Total bilirubin Direct bilirubin Indirect bilirubin Total protein *PT/INR* [a] *Complete blood count with differential* [a] *ALP* [a] *GGT* [a]
Routine urinalysis	Specific gravity pH, glucose, protein, ketones, bilirubin, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	For participants of childbearing potential only: highly sensitive (serum or urine) hCG pregnancy test			
Additional testing	Genetic testing for *SCN1A* [d]			

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; hCG: human chorionic gonadotropin; INR: international normalized ratio; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; PT: prothrombin time; RBC: red blood cell; WBC: white blood cell.

[a] Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1, Section 10.6 and Figure 10a (follow guidance in Section 10.6 on when these additional test are required)

[b] To be performed only at screening.

[d] For participants with DS only: If genetic testing was not performed previously or if the *SCN1A* result is negative (without any other positive gene reported that is consistent clinically with DS), testing for *SCN1A* will be offered at the time of screening, per local restrictions

10.2.1 Clinical Laboratory Assessments and Other Safety Assessments

A change in the value of a clinical laboratory parameter, physical examination finding, or a vital sign measure can represent an AE if the change is clinically relevant or if, during administration of study drug, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the study drug, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), physical examination, or vital signs that were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the participant, whether a change in a clinical laboratory value, physical examination, or vital sign parameter is clinically significant and represents an AE. The assessment of clinical significance is recorded on the eCRF related to the assessment (for example, the clinical laboratory value eCRF), but an event that is also classified as an AE will be recorded on the AE page.

10.2.2 Biological Sample Retention and Destruction

Not applicable. There will be no collection, storage and future use of biological samples from clinical study participants in this study.

10.3 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Table 10.b AE Subtypes Defined in This Section

Type	Nested Subtypes	Report Within [a]	Sponsor Reports [b]
AE – collection timing per SoA—Section 1.3		NE	NE
	AESI—Section 8.3.8.7, Section 10.3.3.2	24 hours	TBD [c]
	Pretreatment emergent	NE	NE
	TEAE—Section 10.3.4.9	NE	NE
	SAE—Section 8.3.8.4	24 hours	TBD [c]
	Related AE—any study drug (whether the investigational product or another drug)— Section 6.1, Section 10.3.4.3	NE	NE
	Related AE (ADR) (related to the investigational product)	NE	NE
	Expected AE—Section 10.3.4.7	NE	NE
	Unexpected AE—Section 10.3.4.8	NE	NE
	SSR	7 days	NE
	SUSAR (ie, related to investigational product)—Section 10.3.5.2		
	• Fatal/life-threatening	24 hours	7 days
	• Nonfatal/non–life-threatening	24 hours	15 days

ADR: adverse drug reaction; AE: adverse event; AESI: adverse event of special interest; NE: not expedited; SAE: serious adverse event; SSR: special situation reporting; SUSAR: suspected, unexpected serious adverse reaction; TBD: to be determined; TEAE: treatment-emergent adverse event.

The specific timeframes on this chart apply to expedited AE/SAE reporting periods and procedures for which this protocol provides additional instructions. reporting via the eCRF is *required but is not sufficient* to expedite a report.

[a] This is the required, expedited reporting period for the site to report the event to the sponsor/contract research organization.

[b] This is the required, expedited reporting period for the sponsor to notify other parties including but not limited to regulatory agencies. For some studies, partner agreements may exist that have different reporting timelines, as specified in the individual pharmacovigilance agreement.

[c] To be evaluated by sponsor. Reporting requirements vary.

10.3.1 Definition of AE

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of the study drug, whether or not the occurrence is considered related to the study drug.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study drug.

An untoward finding generally may necessitate therapeutic drug, require an invasive diagnostic procedure, or require discontinuation or a change in dose of study drug or a concomitant medication. (Repeated or additional noninvasive testing [eg, laboratory or electrocardiogram (ECG) retests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic drug.)

Events Meeting the AE Definition
• New condition detected or diagnosed after the use of the study drug(s), even though it may have been present before the start of the study. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition. • Event that is of greater intensity, frequency, or duration than expected for the individual participant, or an event with a reasonable possibility that it was related to the study drug. • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, physical examinations, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease), including those that worsen from baseline.
Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction: • An intentional overdose taken with possible suicidal/self-harming intent, regardless of sequelae.
Signs, symptoms, and/or clinical sequelae resulting from a lack of efficacy (NOT the lack of efficacy per se), as long as they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Situations in which an untoward medical occurrence did not occur (eg, preplanned or elective surgery [a]). • Presence or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.[b] • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Cases of overdose with any medication without manifested side effects. [c]

[a] Preplanned and elective surgeries are defined as those that were scheduled before signing of informed consent (see exceptions in Section 10.3.3.1). While these procedures are not considered AEs, they should be documented in the participant's source documents as described in Section 8.1.3.

[b] Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Likewise, baseline evaluations (eg, laboratory tests, ECG, x-rays) should NOT be recorded as AEs unless they are related to study procedures.

[c] Overdoses should be documented in the participant's source documents.

AE onset and resolution dates are defined as follows:

- Start date: the date when the first signs/symptoms were noted by the participant and/or investigator.
- End date: the date when the participant recovered, the event resolved but with sequelae, or the participant died.

10.3.2 Definition of SAE

SAEs are events that meet BOTH the AE criteria described in Section 10.3.1 AND the criteria for seriousness below.

An SAE is defined as any untoward medical occurrence that meets one or more of the criteria listed:

- Results in death.
- Is life threatening.

Note: The term life threatening in the definition of serious refers to an event in which the participant 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.

- Requires inpatient hospitalization or prolongation of existing hospitalization.

  Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity.

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via an authorized medicinal product.
- Other situations:
  - Is an important medical event.
  - May require drug to prevent one of the outcomes listed above.
  - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical drug to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.3 Additional Considerations in Identifying and Defining AEs

10.3.3.1 Defining Discrete AEs

Each reported AE should represent a single diagnosis, if the diagnosis is known. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs UNLESS the diagnosis is unknown. Specific examples are as follows:

Laboratory values and ECG findings:

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis should be reported as the AE.

Worsening of a condition:

If the participant experiences a worsening or complication of a medical condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…"). This includes:

- Pre-existing conditions present at the time of signing of informed consent.
- Pre-existing episodic concurrent medical conditions (eg, asthma, epilepsy): An episode should only be recorded as an AE if the condition becomes more frequent, serious, or severe in nature.
- A degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis): Worsening of the condition should only be recorded as an AE if it occurs to a greater extent than expected.
- Worsening or complication of an AE after any change in study drug: The worsening or complication should be recorded as a new AE.

Complications associated with preplanned procedures:

- Changes in plan and surgical complications associated with preplanned or elective surgeries, therapies, or procedures should be recorded as AEs.
- 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 an elective surgery should be recorded as AEs.

Changes in intensity of AEs:

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

10.3.3.2 AESIs

An AESI (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 to characterize and understand them.

The following events will be reported as AESI for this study:

- 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 participants in the TAK-935-2001 study of adult participants with DEEs. To assess this potential interaction, clinical safety monitoring and expanded evaluation will be performed to closely monitor seizure frequency in these participants.

- 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. (See Section 8.3.4.)

- Psychosis:

During the phase 1 multiple rising dose study in healthy participants, episodes of confusion, euphoria, and psychosis were seen at the highest dose of 600 mg/d. However, in this study participants 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 10.3.4.

AESIs must be recorded as AEs in the eCRF within 24 hours. An evaluation form along with all documentation must be submitted to the sponsor.

10.3.4 Recording and Follow-up of AE and/or SAE

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information. Each event must be categorized in terms of the attributes below, over the entire course of the event, including the start and stop dates. It is **not** acceptable for the investigator to send photocopies of the participant's source documents to sponsor in lieu of completion of the required form. There may be instances when copies of source documents for certain cases are requested by sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the source documents before submission to sponsor. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.4.1 Frequency

Assessment of Frequency
The investigator should assess and record the frequency of the event. Episodic AEs (eg, vomiting) or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.3.4.2 Intensity

Assessment of Intensity	
The investigator will assess the intensity for each AE and SAE (including any laboratory abnormality) reported during the study and assign it to one of the following categories:	
Mild:	An AE that is usually transient, easily tolerated by the participant, and may require only minimal treatment or therapeutic drug. The event does not generally interfere with usual activities of daily living.
Moderate:	An AE that is usually alleviated with additional specific therapeutic drug. The event causes discomfort and interferes with usual activities of daily living, but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic drug.
Note: Intensity and seriousness are separate concepts. The terms "severe" and "serious" are not synonymous. Because serious events usually pose a threat to a participant's life or ability to function, seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.	

10.3.4.3 Causality/Relatedness

Assessment of Causality	
The investigator must assess the relationship between the study intervention and each occurrence of each AE/SAE based on the criteria below:	
Related:	An AE that follows a reasonable temporal sequence from administration of the study drug(s) (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. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
Not related:	An AE that does *not* follow a reasonable temporal sequence from administration of the study drug(s) and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.
The investigator will also consult the IB and/or product information, for marketed products, in their assessment.	

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.3.4.4 Action Taken

Action Taken Concerning Intervention(s)

The investigator must make note of the action taken concerning the study drug:

- Dose not changed.
- Dose increased.
- Dose reduced.
- Drug interrupted.
- Drug withdrawn.
- Dose delayed.
- All drugs withdrawn.
- Unknown.
- Not applicable (a study drug was stopped for a reason other than the particular AE [eg, the study has been terminated, the participant died, dosing with study drug was already stopped before the onset of the AE]).

For any AE that was ongoing at the time of a participant's death, the study intervention action should reflect the most recent action that had been taken at the time of death (eg, drug interrupted, reduced, withdrawn). If the participant had never received the study intervention, the action taken should be recorded as "dose not changed" or "not applicable." The study intervention action of "withdrawn" should not be selected solely as a result of the participant's death.

10.3.4.5 Outcome

Outcome
The investigator must make note of the outcome of any AEs that occur during the course of the study: • Recovered/resolved: The participant returned to first assessment status with respect to the AE. • Recovered/resolved with sequelae: The participant recovered from an acute AE but was left with permanent/significant impairment. • Recovering/resolving: The intensity has decreased by 1 or more stages: the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value has improved, but has not returned to the normal range or to baseline; the participant died from a cause *other than* this particular AE. • Not recovered/not resolved: There is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period is now worse than when it started; is an irreversible congenital anomaly; the participant died from another cause. • Fatal: The AE is considered to be the cause of death or contributed to the participant's death. • Unknown: The course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

10.3.4.6 Follow-up

Follow-up of AEs and SAEs
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology. New or updated information will be recorded in the originally submitted documents. The investigator will submit any updated SAE data to sponsor within 24 hours of receipt of the information.

10.3.4.7 Reference Safety Information

The reference safety information (RSI) for this study is the IB, which the sponsor has provided under separate cover to all investigators.

10.3.4.8 Unexpected AEs

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the RSI. "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but will not be based on what might be anticipated based on the pharmacological properties of a product.

10.3.4.9 TEAEs

As described in Section 1.3, all AEs will be collected from the time when the ICF is signed. For reporting purposes in the study, a TEAE is defined as any event emerging or manifesting at or after the initiation of treatment with a study drug or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the study drug or medicinal product.

10.3.5 Expedited Reporting of SAEs and Selected AEs

This section describes the expedited reporting required for certain types of events, in addition to eCRF completion:

Sites must report SAEs immediately, and in no case in more than 24 hours.

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the medical monitor by telephone. Contacts for SAE reporting can be found in the study operations manual.

SAE Reporting to the Sponsor via a Paper Data Collection Tool
If the electronic system is unavailable, then the site will use the paper data collection tool to report the event within 24 hours. Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames. If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information. Information in the SAE report or form must be consistent with the data provided on the eCRF. Contacts for SAE reporting can be found in the study operations manual.

10.3.5.1 Reporting of Abnormal Liver-Associated Test Results

Refer to Section 8.3.8.4.1 and follow the additional monitoring, evaluation, and follow-up recommendations in Section 10.6.

10.3.5.2 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for identifying and reporting all SUSARs and any other applicable SAEs to regulatory authorities, investigators, and IRB or IEC in accordance with national regulations in the countries where the study is conducted. AEs that are already classified as expected (and therefore are not SUSARs) are listed in the RSI, See Section 10.3.4.7 for the location of the RSI.

The following specialized types of events have their own reporting windows:

- SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, relative to the first awareness of an event by/or further provision to the sponsor or sponsor's designee, unless otherwise required by national regulations.
- The sponsor will prepare an expedited reports for other safety issues that 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 study.

The study site will forward a copy of all expedited reports to its IRB or IEC in accordance with local regulations.

10.3.6 Reporting of Non-SAEs Related to Auxiliary Medicinal Products

Not applicable.

10.4 Contraceptive and Barrier Guidance

10.4.1 Definitions

For the purposes of this study, reproductive status is defined as follows:

- **Nonpregnant:** Negative urine and/or serum beta human chorionic gonadotropin (hCG) pregnancy test result.
- Person who is not of childbearing potential:
  - Premenarchal and 1 of the following:
    - Tanner stage 1.
    - <9 years of age.
  - Surgically sterile for at least 6 weeks at screening (defined as having undergone one of the following procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy).
  - Postmenopausal at screening (defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal

contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Person who ***is*** **of childbearing potential**: following menarche and until becoming postmenopausal unless permanently sterile by the definition above.
- Male who **is not fertile**: Sterilized males should be at least 1 year after a bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.
- Male who ***is*** **fertile**: postpuberty, unless permanently sterile by the definition above.

10.4.2 Contraception Guidance

In this study, the use of effective (not applicable for Germany) or highly effective contraception is generally required unless otherwise noted. In addition, contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

The failure rates of contraceptives that are used consistently and correctly may differ in typical use. Therefore, when study participation requires any of these methods of contraception to be used, participants must commit to using them:

- Consistently throughout the required period.
- Correctly, as described below and in any labeling associated with the method.

Contraception requirements depend in part on the reproductive status of the participant and the participant's partner.

Table 10.c Acceptable Contraception Methods and Lactation Guidance for This Study

Highly Effective Contraceptives **Failure rate of <1% per year when used consistently and correctly**	**Effective Contraceptives a** **Failure rate of >1% per year when used consistently and correctly**
User Dependent	
• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. [b,c] – Oral. – Intravaginal. – Transdermal. • Progestogen only hormonal contraception associated with inhibition of ovulation. – Oral. – Injectable. • Sexual abstinence. [d] • Refraining from donating sperm. [e]	• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. • Male or female condom with or without spermicide. [f] • Cap, diaphragm or sponge with spermicide. [f] • Combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods).
Low User Dependency	
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation. [a,b] • IUD. • IUS. • Bilateral tubal occlusion. • Vasectomy; vasectomized partner. [g,h]	
Measures Intended to Prevent Fetal and Neonatal Exposure via Sperm or Breastmilk	
• Participants who are lactating must agree not to use their breastmilk to feed an infant.	

IUD: intrauterine device; IUS: intrauterine hormone-releasing system

[a] Effective method of contraception is not applicable in Germany.

[b] Hormonal contraceptives must be stabilized for at least 30 days before the start of the screening period.

[c] Hormonal contraception may be susceptible to interaction with the intervention, which may reduce the efficacy of the contraceptive method. Therefore, 2 highly effective methods of contraception should be used during the treatment period and for at least 30 days after the last dose of study treatment.

[d] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Table 10.c Acceptable Contraception Methods and Lactation Guidance for This Study

Highly Effective Contraceptives **Failure rate of <1% per year when used consistently and correctly**	**Effective Contraceptives a** **Failure rate of >1% per year when used consistently and correctly**

[e] Refrain from donating sperm for the duration of the study and within 90 days following the last administration of the study drug.

[f] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[g] A vasectomy is a highly effective contraceptive method *only if* the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

[h] For participants of childbearing ability, having a vasectomized partner is a highly effective contraception method provided that the partner is the participant's sole partner and that the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Table 10.d Unacceptable Contraception Methods

Methods that are unacceptable in *any* study requiring contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (*coitus interruptus*) • Spermicides only • Lactational amenorrhea method • Use of both female condom and male condom together at the same time
Contraceptives that are effective but have a failure rate of >1% per year when used consistently and correctly are unacceptable in a study requiring *highly effective contraception (ie, <1% failure rate)*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm or sponge with spermicide

From signing of the ICF and throughout the duration of the study and for 30 days after the last dose, participants of childbearing potential (ie, nonsterilized, premenopausal participants) who are sexually active must use acceptable methods of contraception.

Also, from signing of the ICF, throughout the duration of the study, and for 90 days after last dose, nonsterilized male participants who are sexually active with a partner of childbearing potential must use contraception.

Participants will be provided information on acceptable methods of contraception as part of the participant informed consent process and will be asked to sign an ICF stating that they understand the requirements for avoidance of pregnancy during the study. During the study, regular urine hCG pregnancy tests will be performed, and participants will receive continued

guidance on avoiding pregnancy. At investigator discretion serum (hCG) pregnancy tests can be performed at any time during the study (and can be performed instead of urine).

Female participants of childbearing potential must have a negative urine pregnancy test at screening (serum hCG pregnancy test can be performed at investigator discretion) at screening (Visit 1). A pregnancy test at randomization (Visit 2) is not required for eligibility if performed and confirmed negative at Visit 1 and if the investigator does not deem it necessary to repeat pregnancy test at Visit 2.

In addition, male participants must be advised not to donate sperm from signing of the ICF to 90 days after the last dose of study drug.

10.4.3 Pregnancy

If any participant is found to be pregnant during the study, the participant should be withdrawn and sponsor-supplied intervention should be immediately discontinued.

If a participant's partner becomes pregnant during the study or for 30 days after the last dose, the participant's partner should be asked for consent to record and follow the pregnancy.

If the pregnant participant or the participant's pregnant partner agrees, the investigator should notify their primary care physician that the participant/participant's partner was participating in a clinical study when they became pregnant and provide details about the drug the participant received (blinded or unblinded, as applicable).

If the pregnancy occurs during administration of active study intervention (eg, after Visit 1) or within 90 days after the last dose of active study drug, the pregnancy should be reported immediately.

All pregnancies in participants or their partners will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

10.5 Genetics

Not applicable.

10.6 Abnormal Liver-Associated Test Result Monitoring and Follow-up Assessments and Study Drug Restart/Rechallenge Guidelines

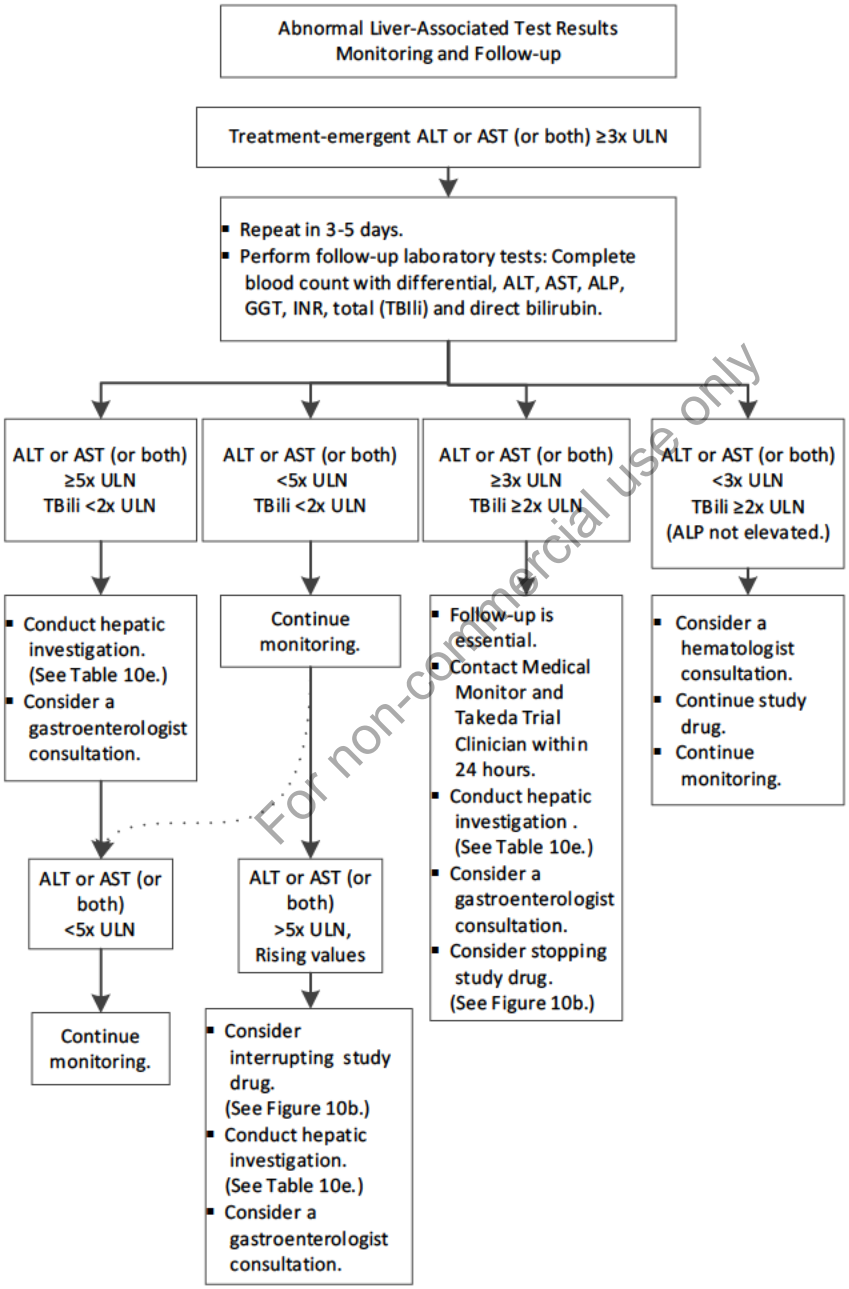
Investigators must be vigilant for abnormal liver-associated test results in participants during the clinical study. Transient fluctuations in serum aminotransferases occur commonly in clinical study participants, but it is crucial that the investigator identifies and evaluates participants with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver-associated test results in clinical study participants who had no known liver disease and had either normal or near normal baseline liver test results (ie, ALT <2 × ULN, total bilirubin <1.5 × ULN, and alkaline phosphatase <1.5 × ULN) at the time (before) of enrollment (during screening period).

In evaluating study participants with abnormal liver-associated test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the participant. If the abnormal liver-associated test results are confirmed, then the participant should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 10.a. Suggested hepatic investigations are listed in Table 10.e. Criteria for considering discontinuation of study drug are shown in Figure 10.b.

Participants With Combined Elevations in Aminotransferase(s) and Bilirubin

If a participant has elevated ALT >3 × ULN with **concurrent** elevated total bilirubin >2 × ULN **or** elevated INR >1.5, the investigator must contact the medical monitor and Takeda study clinician within 24 hours. Hepatic investigations as suggested in Table 10.e should be initiated. Any event of elevated ALT >3 × ULN with concurrent elevated total bilirubin >2 × ULN or elevated INR >1.5 for which an alternative etiology has not been identified must be reported as an SAE.

Figure 10.a Abnormal Liver-Associated Test Results: Monitoring and Follow-up

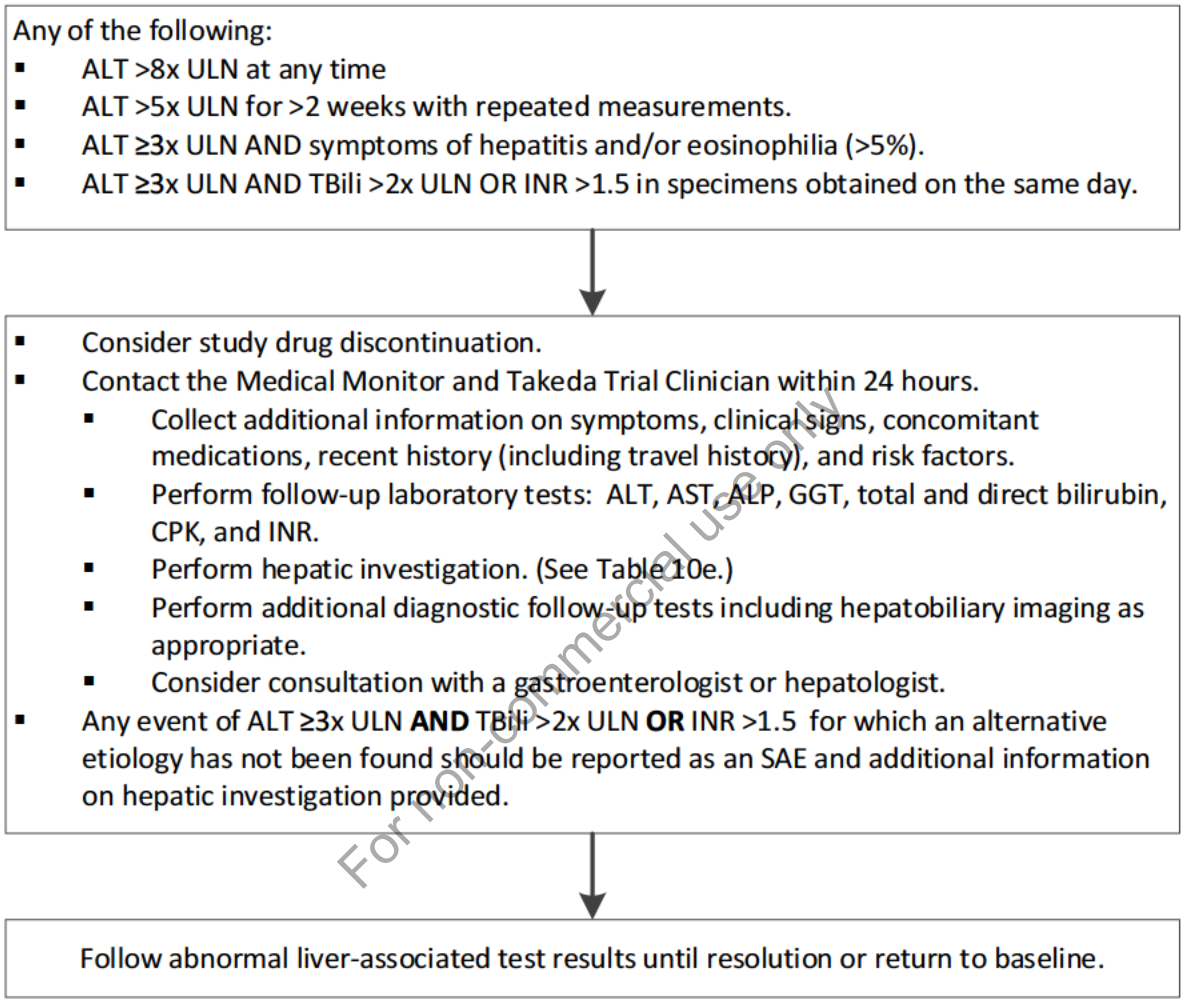


ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; TBili, total bilirubin; ULN, upper limit of normal.

Table 10.e Hepatic Investigation

Medical history	• Concomitant medications (including over-the-counter medications, such as acetaminophen, and herbal supplements). • Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis). • Alcohol intake. • Hepatobiliary disorder. • Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia). • Travel history.
Physical examination (symptoms, signs, and laboratory results)	• General malaise, fatigue, nausea, or vomiting. • Right upper quadrant pain or tenderness, fever, jaundice, rash. • Eosinophilia >5%.
Hepatic/hepatobiliary imaging	Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging).
Viral hepatitis serology	• Hepatitis A antibody (total and IgM). • Hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (anti-HBs), Hepatitis B core antibody (IgM anti-HBc), hepatitis C antibodies (anti-HCV). • Hepatitis E (IgG and IgM). • Consider polymerase chain reaction for hepatitis B, C, and E. • Consider Epstein-Barr virus serology (viral capsid antigen, nuclear antigen, early antigen). • Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	• Anti-nuclear antibody. • Anti-smooth muscle antibody. • Anti-liver-kidney microsomal antibody).

Figure 10.b Abnormal Liver-Associated Test Results: Considerations for Study Drug Discontinuation



ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; INR: international normalized ratio; TBilli: total bilirubin; ULN: upper limit of normal.
Note: For AST >3 × ULN, follow the same procedures as in the figure.

10.7 Country-Specific Requirements

Not applicable.

10.8 Abbreviations and Definitions

10.8.1 Abbreviations

24HC	24*S*-hydroxycholesterol
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARCADE	TAK-935-18-002
ASM	antiseizure medication
AST	aspartate aminotransferase
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
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
CH24H	cholesterol-24-hydroxylase
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	Clinical Trials Regulation
CYP	cytochrome P450
DEE	developmental epileptic encephalopathy
DS	Dravet syndrome
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
ELEKTRA	TAK-935-2002
ENDYMION 1	TAK-935-18-001
ENDYMION 2	TAK-935-3003
EO	enzyme occupancy
EQ-5D-5L	EQ-5D 5-level version
EQ VAS	EQ-5D visual analogue scale
ET	early termination

EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-tube	gastrostomy tube
hCG	human chorionic gonadotropin
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
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
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QI-Disability	Quality of Life Inventory-Disability
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SOC	standard of care
SSR	special situation reporting
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

US	United States
VNS	vagus nerve stimulation

10.9 Protocol Amendment History

Date	Amendment Number	Region
10 March 2023	Initial version	Global
27 June 2023	Amendment 1	Global

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Appendix 1 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 18 January 2023.)

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

Appendix 2 Blood Volumes

The amount of blood from participants at all scheduled visits during the study will be volumes not exceeding 2.4 mL/kg during any 4-week period. Additional blood may be drawn for retests and unscheduled visits, if any, and will not exceed 2.4 mL/kg of body weight during any 4-week period. Topical anesthetics are allowed (if necessary) for the collection of samples. Site will be advised not to collect samples on same day if failed twice. Another attempt can be made after 2 to 4 weeks.

The approximate blood volume collected at each visit and total blood volume during the study by weight will be captured in reference materials eg local laboratory documentation.

These volumes represent the approximate maximum for visit and weight. Sites will be advised not to attempt collection of blood if they fail twice. Another attempt can be made after 2 to 4 weeks.

Appendix 3 Minimizing Stress and Pain for Study Participants

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 participants.

For both adult and pediatric participants, the risk associated with the administration of soticlestat is low, because 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 rescue ASMs to be used during the study.

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, and optional genetic testing, do not have significant risks or burdens and are designed to collect critical information on AESIs, 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 it is easier to access veins that are small or narrow. Butterfly needles with smaller size (23 gauge) are used in participants weighing ≤45 kg, while 21 gauge are used in participants weighing > 45 kg. Sites will be advised not to attempt collection of blood if they fail twice. Blood volume collected has been minimized based on weight in children, as specified in Appendix 2.

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. In addition, in jurisdictions where home visits by site staff in clinical studies are allowed per the discretion of the investigator and permissible by local regulations, home visits 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.

Signature Page for TAK-935-3004 Protocol Amendment 1

Title: Amendment 1 to An Open-label, Nonrandomized, Phase 3 Study to Evaluate th

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Approval	[redacted] Statistics 28-Jun-2023 17:33:35 GMT+0000

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