Clinical Study Protocol

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Title: Phase 1 Pharmacokinetics and Safety Study of Oral Soticlestat in Participants with Moderate or Mild Hepatic Impairment and Normal Hepatic Function

Study Number: TAK-935-1010

Document Version and Date: Amendment 1; 11 April 2022

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TAKEDA PHARMACEUTICALS

PROTOCOL

Phase 1 Pharmacokinetics and Safety Study of Oral Soticlestat in Participants with Moderate or Mild Hepatic Impairment and Normal Hepatic Function

Study Identifier: TAK-935-1010

Compound: Soticlestat (TAK-935)

Sponsor: Takeda Development Center Americas, Inc.
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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, MA 02421 Telephone: +1 (617) 679-7000	Soticlestat (TAK-935)
Study Identifier: TAK-935-1010	**Phase:** 1

Protocol Title: Phase 1 Pharmacokinetics and Safety Study of Oral Soticlestat in Participants with Moderate or Mild Hepatic Impairment and Normal Hepatic Function

Study Design:

This is a phase 1, open-label, study of oral soticlestat designed to assess the pharmacokinetics (PK) of single dose soticlestat [redacted] in participants with moderate or mild hepatic impairment (HI) compared to matched healthy participants with normal hepatic function. At least 12 healthy participants (up to 24 participants) with normal hepatic function will be recruited to match the group mean of moderate and mild HI arms by age (mean ± 10 years), sex (± 2 per sex), and body mass index (BMI, mean ± 10%). Eight (8) participants will also be enrolled in each HI arm of the study according to the following criteria:

- Arm 1: (N = 8): Moderate HI (Child-Pugh Class B [Score: ≥ 7 and ≤ 9]), 300 mg single dose
- Arm 2: (N = 8): Mild HI (Child-Pugh Class A [Score: ≥ 5 and ≤ 6]), 300 mg single dose
- Arm 3: (N = 12-24): Normal hepatic function, 300 mg single dose

The study will consist of a 28-day screening period (prior to dosing) and a 7-day confinement period (Day -1 to Day 7).

Two hepatic function assessments are required prior to Day 1 dosing for participants with HI. These 2 assessments should be obtained during the screening period and at least 48 hours apart. In the case where a participant has an available historical Child-Pugh assessment score within 3 months prior to screening, 1 assessment can be conducted during the screening period. If the Child-Pugh scores from these 2 assessments indicate the same liver function category for the participant (ie, normal hepatic function, moderate HI, or mild HI), soticlestat can be administered as scheduled. If the results of the 2 assessments indicate different liver function categories, a third assessment must be conducted at least 24 hours after the second assessment. If the results of the 2 most recent assessments (the second and third) are in agreement with regard to the participant's liver function category, the participant may be enrolled and should receive the Day 1 dose within 48 hours of the third assessment. If the second and third measurements differ, the participant will not be eligible for the study.

The moderate HI arm (ie, Arm 1) will be conducted first, followed by 12 participants in the matched normal hepatic function arm (Arm 3). After all participants in the moderate HI arm and the matching 12 participants in the matched normal hepatic function arm have completed the treatment period, an informal interim PK data analysis is planned and may additionally leverage historical control PK data in healthy participants to gain an initial estimate of the effect of moderate HI on the PK of soticlestat [redacted].

Following completion of enrolment of the mild HI arm, and in the instance any of the previously enrolled healthy participants cannot be used for matching purposes, up to an additional 12 participants may be enrolled for the matched normal hepatic function group (Arm 3) to ensure a minimum of 12 participants with normal hepatic function and matching the mean of the mild HI arm by age (mean ± 10 years), sex (± 2 per sex), and body mass index (BMI, mean ± 10%) are enrolled.

Participants will receive a single oral dose of 300 mg soticlestat as three 100 mg T4 tablets on Day 1 with approximately 240 mL water under fasting conditions. PK samples will be collected from Days 1 to 7, at predetermined time points (Section 3.0), to characterize the PK of soticlestat [redacted] in participants with moderate or mild HI compared to matched healthy participants with normal hepatic function (Section 3.0).

Participants will remain in the clinic throughout the study. Participants will be discharged from the clinic on Day 7 after the last PK sample collection and study procedures are completed. A safety follow-up contact for all participants (including those who terminate the study early) will occur 14 ± 2 days after the soticlestat dose to determine if any AEs have occurred since clinical research unit (CRU) discharge.

Study Primary Objective:

- To characterize the plasma PK of soticlestat following a single oral dose in participants with moderate or mild HI compared to matched healthy participants with normal hepatic function.

Study Secondary Objective:

- To evaluate the safety and tolerability of soticlestat following a single oral dose in participants with moderate or mild HI as well as matched healthy participants with normal hepatic function.

[redacted]

Study Participant Population: Healthy male and female participants and participants with moderate and mild HI aged ≥ 18 to < 75 years and with a BMI ≥ 18.0 and ≤ 40.0 kg/m^2 at screening (at least 50% of the participants will be required to be of BMI ≥ 18.0 and ≤ 35.0 kg/m^2). Healthy participants will be matched to hepatic impaired participants in this study by age (mean ± 10 years), sex (± 2 per sex), and BMI (mean ± 10%).

Planned Number of Participants:	**Planned Number of Sites:**
Up to 40 participants will be enrolled: 8 participants with moderate HI 8 participants with mild HI 12 to 24 participants with normal hepatic function	Up to 7 clinical sites
Dose Level: 300 mg soticlestat (3 x 100 mg T4 tablets).	**Route of Administration:** Oral
Duration of Treatment: Single-dose on Day 1	**Planned Study Duration:** Approximately 42 days including screening period and follow-up.

Criteria for Inclusion:

Inclusion for Participants with Hepatic Impairment

Participants must fulfill the following inclusion criteria to be eligible for participation in the study (participants who do not qualify based on a reversible condition or mild intercurrent illness may be re-screened after the condition is resolved. Screening tests may be repeated if in the Investigator's opinion the test needs to be repeated):

1. Is an adult male or female participant aged ≥ 18 to < 75 years, at screening.
2. Has a BMI ≥ 18.0 and ≤ 40.0 kg/m^2, at screening. At least 50% of the participants will be required to be of BMI ≥ 18.0 and ≤ 35.0 kg/m^2, at screening.
3. Aside from HI, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, ECGs, and screening clinical laboratory profiles, as deemed by the Investigator or designee.
   - Supine blood pressure (BP) is ≥ 80/40 mmHg (asymptomatic) and ≤ 150/95 mmHg, at screening;
   - Supine pulse rate (PR) is ≥ 40 bpm and ≤ 99 bpm, at screening;
   - QT interval corrected for PR using Friderica's formula (QTcF) is ≤ 500 msec and electrocardiogram (ECG) findings considered normal or not clinically significant by the Investigator or designee, at screening.
4. The participant must have had chronic HI for at least 3 months before screening, and the HI must be stable, ie, no

significant changes in hepatic function in the 30 days preceding screening (or since the last visit if within 6 months before screening) and treatment with stable doses of medication. Has a score on the Child-Pugh Class at screening as follows:

- (Arm 1) Moderate HI, Child-Pugh Class B: ≥ 7 and ≤ 9
- (Arm 2) Mild HI, Child-Pugh Class A: ≥ 5 and ≤ 6

5. Participants should not have renal dysfunction as demonstrated by a relatively adequate renal function (creatinine clearance ≥ 50 mL/min), at screening.

Inclusion for Healthy Participants

Participants must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Is an adult male or female participant aged ≥ 18 to < 75 years, at screening. Healthy participants will be matched to hepatic impaired participants in this study by sex (± 2 per sex) and by age (mean ± 10 years).
2. Has a BMI ≥ 18.0 and ≤ 40.0 kg/m^2, at screening. At least 50% of the participants will be required to be of BMI ≥ 18.0 and ≤ 35.0 kg/m^2, at screening. Healthy participants will be matched to hepatic impaired participants in this study by BMI (mean ± 10%).
3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
   - Supine BP is ≥ 90/40 mmHg and ≤ 150/95 mmHg, at screening;
   - Supine PR is ≥ 40 bpm and ≤ 99 bpm, at screening;
   - QTcF is ≤ 450 msec (males) or ≤ 470 msec (females) and ECG findings considered normal or not clinically significant by the Investigator or designee, at screening;
   - Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin ≤ the upper limit of normal (ULN) at screening and check-in.
4. Participants should not have renal dysfunction as demonstrated by a relatively adequate renal function (creatinine clearance ≥ 60 mL/min), at screening.

Inclusion for Participants with Hepatic Impairment and Healthy Participants

Participants must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Understands the study procedures in the informed consent form (ICF), provides a signature/date in the ICF, and is willing and able to comply with the protocol.
2. Continuous non-smoker or moderate smoker (≤ 10 cigarettes/day or the equivalent) before screening. Participant must agree to consume no more than 5 cigarettes or equivalent/day from the 7 days prior check-in and until discharge from the CRU.
3. Female participants of childbearing potential and male participants agree to comply with any applicable contraceptive requirements of the protocol as detailed in Appendix D.

Criteria for Exclusion:

Exclusion for Participants with Hepatic Impairment:

The participant must be excluded from participating in the study if the participant:

1. Has history or presence of clinically significant medical or psychiatric condition or disease (aside from HI) or presence of psychotic disorders such as psychosis, delusions, or schizophrenia in the opinion of the Investigator or designee.
2. Has a history of liver or other solid organ transplant.
3. Has history or presence of alcoholism and drug abuse within the past 6 months prior to dosing.
4. Positive result at screening for human immunodeficiency virus (HIV). Hepatitis B surface antigen (HBsAg) positive participants are allowed to be enrolled if hepatitis B virus (HBV) deoxyribonucleic acid (DNA) is below 1000 copies/mL in the plasma. Participants with moderate or mild HI who are positive for anti-HCV antibody (HCVAb) can be enrolled but must not have detectable HCV ribonucleic acid (RNA) in the plasma.

Exclusion for Healthy Participants

The participant must be excluded from participating in the study if the participant:

1. Has history or presence of clinically significant medical or psychiatric condition or disease or presence of psychotic disorders such as psychosis, delusions, or schizophrenia in the opinion of the Investigator or designee.
2. Has history or presence of alcoholism and drug abuse within the past 2 years prior to dosing.
3. Positive results at screening for HIV, HBsAg, or hepatitis C virus (HCV).

Exclusion for Participants with Hepatic Impairment and Healthy Participants

The participant must be excluded from participating in the study if the participant:

1. Has history of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
2. Has history or presence of clinically significant hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
3. Has positive results for the urine or saliva drug screen at screening or check-in, unless the positive drug screen is due to prescription drug use that is approved by the Investigator (cannabinoids can be used for medicinal use at the discretion of the Investigator).
4. Is a female with a positive pregnancy test or who is lactating.
5. Has positive results for urine or breath alcohol screen at screening or check-in.
6. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 7.3 (Excluded Medications, Supplements, Dietary Products) for the prohibited time period.
7. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing.
8. Has made a donation of blood or had significant blood loss within 56 days prior to dosing.
9. Has made a plasma donation within 7 days prior to dosing.
10. Participated in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.
11. Any positive responses on the Columbia-Suicide Severity Rating Scale (C-SSRS) or has a risk of suicide according to the Investigator's judgment based on the assessment of the C-SSRS at screening or check-in or has made a suicide attempt in the previous 12 months prior to dosing.

Main Criteria for Evaluation and Analyses:

Primary endpoints:

The following PK parameters in plasma will be analyzed for soticlestat:

- Maximum observed concentration (C_{max})
- Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞})
- Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last})

Secondary endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of clinically significant abnormal values for laboratory evaluations, vital signs, ECG parameters, and C-SSRS

[redacted]

Statistical Considerations:

Pharmacokinetics:

Descriptive statistics will be used to summarize concentrations of soticlestat and PK parameters according to hepatic function group (normal hepatic function and moderate and mild HI). An analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed C_{max}, AUC_{last}, and AUC_{∞} for soticlestat to compare each HI group with the normal hepatic function group, and 90% confidence intervals (CI) for the ratio of geometric means from each HI group versus normal function group will be provided. The addition of other factors and covariates such as age, sex, and BMI on the relationship between soticlestat PK parameters and level of HI may also be investigated.

Descriptive statistics will be used to summarize concentrations of [redacted] PK parameters according to hepatic function group (normal hepatic function and moderate and mild HI).

The fraction of unbound soticlestat will be determined.

Safety:

TEAEs will be tabulated. Summary statistics for vital signs, safety 12-lead ECGs, C-SSRS, and safety laboratory assessments will be computed and provided according to hepatic function group (normal hepatic function and moderate and mild HI). Markedly abnormal values (MAV) criteria for vital signs, 12-lead ECGs, and safety laboratory assessments will be defined in the statistical analysis plan (SAP).

Sample Size Justification:

The planned sample size of 8 participants in each HI arm is not based on power calculations and is considered adequate to provide a descriptive characterization of the PK of soticlestat [redacted] in participants with moderate or mild HI compared to healthy participants with normal hepatic function.

Any participant who is not PK evaluable including those experiencing emesis within 8 hours post dose may be replaced at the discretion of the Investigators in consultation with the Sponsor to ensure 8 PK-evaluable participants in each arm of participants with HI and 12-24 PK-evaluable participants in matched participants with normal hepatic function complete.

2.0 STUDY SCHEMATIC

Table 2.a Study Design for Arms 1, 2, and 3

Screening	Check-in and Predose Assessments [a]	Soticlestat Dosing, PK Sampling and Study Assessments	PK Sampling and Study Assessments	PK Sampling, Study Assessments and Study Discharge[b]	Follow-up
Within 28 days prior to soticlestat dosing	Day -1	Day 1	Days 2-6	Day 7	14 ± 2 days following the soticlestat dose
Outpatient Visit	----------Confinement[a]----------				**(Phone Contact)**

[a] Participants will start the confinement on Day -1 and remain confined in the clinic throughout the study until Day 7. Participants may be admitted to the clinic earlier for Coronavirus Disease-19 (COVID-19) procedures not related to the study protocol. Participants will be discharged from the clinic on Day 7 after the last PK sample collection and study procedures are completed.
[b] Study Discharge is defined as end of treatment and study procedures.

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedures [a]		**Study Days in Arms 1, 2, and 3**																				
Days in Period →	S [b]	**-1**	**1**													**2**		**3**	**4**	**5**	**6**	**7 (EOS)/ET**	**FU** [c]
Hours →		**C-I** [d]	**0**	**0.133**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**14**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Safety Evaluations																							
Full Physical Examination [e]	X	X [f]																				X [g]	
Height	X																						
Weight	X																						
Child-Pugh Assessment [h]	X																						
12-Lead Safety ECG [j]	X	X [i]								X						X						X [g]	
Vital Signs (PR and BP) [j]	X	X [i]								X						X						X [g]	
Vital Signs (RR and T) [j]	X	X [i]														X						X [g]	
Hem, Coag, Serum Chem [k], and UA	X	X																X				X [g]	
Serum Pregnancy Test (♀ only)	X	X																					
Serum FSH (♀ only)	X																						
Urine/Saliva Drug Screen	X	X																					
Urine/Breath Alcohol Screen	X	X																					
HIV/Hepatitis B and C Screen	X																						
C-SSRS [l]	X	X																				X [g]	
AE Monitoring											X												X
ConMeds Monitoring											X												
Study Drug Administration / PK																							
Soticlestat Administration			X [m]																				
Blood for Soticlestat [redacted]			X [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [g]	
[redacted]																							

Study Procedures [a]		**Study Days in Arms 1, 2, and 3**																				
Days in Period →	S [b]	**-1**	**1**												**2**	**3**	**4**	**5**	**6**	**7 (EOS)/ET**	**FU** [c]
Hours →		**C-I** [d]	**0**	**0.133**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**14**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	
Other Procedures																						
Confinement in the CRU [o]		X																				
Visit	X																					

a For details on Procedures, refer to Section 9.0.

b Within 28 days prior to the study drug administration.

c The clinic will contact all participants (including participants who terminate the study early) by phone 14 ± 2 days after the soticlestat administration to determine if any AEs have occurred since CRU discharge.

d Participants will be admitted to the CRU on Day -1 at the time indicated by the CRU. Participants may be admitted to the CRU earlier for COVID-19 procedures not related to the study protocol.

e Symptom-driven physical examinations may be performed during the study, at the Investigator's or designee's discretion.

f If the screening assessment was conducted within 4-7 days prior to dosing (Day 1), assessment will be conducted at check-in only if, in the opinion of the Investigator or designee, there is reason to believe they have substantially changed.

g To be performed at Day 7 (EOS) or prior to ET from the study.

h Two hepatic function assessments are required prior to Day 1 for participants with HI. These 2 assessments should be obtained during screening and at least 48 hours apart. In the case where a participant has an available historical Child-Pugh assessment score within 3 months prior to screening, 1 assessment can be conducted during the screening period. If the Child-Pugh scores from these 2 assessments indicate the same liver function category for the participant (ie, normal function, moderate impairment, or mild impairment), soticlestat can be administered as scheduled. If the results of the 2 assessments indicate different liver function categories, a third assessment must be conducted at least 24 hours after the second assessment. If the results of the 2 most recent assessments (the second and third) are in agreement with regard to the participant's liver function category, the participant may be enrolled and should receive the Day 1 dose within 48 hours of the third assessment. If the second and third measurements differ, the participant will not be eligible for the study.

i To be performed within 24 hours prior to dosing.

j All assessments will be performed (supine position) after participants have rested for at least 5 minutes.

k Samples for serum chemistry will be obtained in the fasted state following a fast of at least 8 hours, however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

l At screening, the C-SSRS Baseline/Screening version will be administered; at all other time points, the Since Last Visit version will be administered. When possible, it is highly recommended that assessments are conducted by the same rater to ensure consistency.

m After an overnight fast of at least 10 hours, soticlestat will be administered. During the first 4 hours after drug administration, no food is allowed.

n Prior to soticlestat administration.

- Participants will start the confinement on Day -1 and remain confined in the clinic throughout the study until Day 7. Participants will be discharged from the CRU on Day 7 after the last PK sample collection and study procedures are completed.

Abbreviations: ♀ = Females, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = Coagulation, ConMeds = Concomitant medication, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = Electrocardiogram, EOS/ET = End-of-Study or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, PK = Pharmacokinetics, PR = Pulse rate, RR = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis.

4.0 INTRODUCTION

4.1 Background

4.1.1 Soticlestat (TAK-935)

Soticlestat is a potent and selective cholesterol 24*S* hydroxylase (CH24H) inhibitor currently in development as an oral adjunct to standard of care therapy for the treatment of rare pediatric epilepsies referred to as Developmental and Epileptic Encephalopathies (DEE) which are a cluster of pediatric epilepsy syndromes and includes Dravet Syndrome (DS) and Lennox Gastaut Syndrome (LGS). Epilepsy is linked to a dysregulation in glutamatergic signaling brought upon by an over-activation of CH24H. This enzyme is predominantly expressed in neurons and involved in the homeostasis of brain cholesterol by converting it to 24*S*-hydroxycholesterol (24HC), a polar metabolite capable of passing the brain barrier via lipoproteins.

Soticlestat is a first-in-class therapeutic candidate that has the potential to control seizures in treatment-resistant patients with epilepsy by reducing over-activated glutamate signaling by modulating reactive astrocytes and reducing over-activated glutamate signaling in neurons. This mechanism of action is thought to clinically manage seizures by reducing seizure frequency and severity as well as brain damage and cognitive deficits that are pathological sequelae of the epileptogenic process but also other conditions where excessive glutamatergic signaling activity drives the pathology.

[redacted]

4.1.1.2 Clinical Safety and Pharmacokinetics

The PK, safety, tolerability, and/or efficacy of soticlestat have been evaluated in 6 phase 1 clinical studies in healthy participants (completed), a phase 1b/2a study in participants with DEEs (completed), and 3 phase 2 studies in participants with DS, LGS, 15q11-q13 duplication syndrome (Dup15q), cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD), or complex regional pain syndrome (completed). One (1) phase 2 open-label, long-term study in participants with various DEEs, including DS, LGS, Dup15q, or CDD, 2 phase 1 drug-drug interaction studies in healthy subjects, 1 phase 1 study in participants with mild to moderate HI and healthy participants, and 3 phase 3 studies in DS and LGS patients are ongoing.

Overall, 382 participants have been enrolled in the clinical trials with soticlestat, of which 341 have received active treatment based on actual exposure and enrollment data from completed and ongoing clinical trials as of the safety data cut-off date (19 November 2021).

[redacted]

Soticlestat was rapidly absorbed with a median time of t_{max} of 0.25 to 0.52 hours following single-dose administration (15 to 1350 mg; Study TAK-935-101) and a median t_{max} of 0.33 to 0.5 hours following multiple dose administration (100 to 600 mg) under fasting conditions in healthy participants (Study TAK-935-1002). When administered under fed conditions, soticlestat t_{max} was delayed by about 1.5 hours and C_{max} was decreased by 60%; however, food had little impact on the total exposure of the drug as AUC decreased by only 11% using the tablet formulation (Study TAK 935-1005). Soticlestat was shown to cross the blood brain barrier and was able to block

tracer binding to the enzyme target demonstrating a sigmoidal maximum observed effect (Study TAK□935-1003). Mean soticlestat $t_{1/2z}$ ranged from 4.39 to 7.16 hours from 200 to 1350 mg following a single-dose administration, and 3.49 to 4.83 hours across the 100 to 600 mg dose range after administration of multiple doses and similar between Days 1 and 14. [redacted].

The PK profile following single-dose and multiple-dose administration were further characterized in healthy Japanese participants (Study TAK-935-1004). Soticlestat was rapidly absorbed after administration, with t_{max} of 0.5 to 0.75 hours. Soticlestat $t_{1/2z}$ values ranged from 5.075 to 8.695 hours after a single-dose and from 2.620 to 3.630 hours after multiple doses with up□titration. PK exposure to soticlestat increased in a greater than dose-proportional manner in the dose ranges from 200 to 1200 mg single dose and 100 to 300 mg BID. Accumulation of 100 BID dosing was minimal for C_{max} and AUC of soticlestat with accumulation ratios less than 1.06 at steady state. [redacted]

4.2 Rationale for the Proposed Study

In this study, the impact of HI on the PK of single dose soticlestat [redacted]. After entering the body, drugs are eliminated by excretion and/or metabolism. Although elimination can occur through a variety of routes, most drugs are cleared by metabolism in the liver and/or small intestine and/or by elimination of unchanged drug by the kidney. Liver disease is associated with several pathophysiologic changes that may alter the PK of a drug. These include alterations in hepatic blood flow, changes in liver enzyme activity, decreased binding of drug to plasma proteins, and impaired biliary excretion [2, 3]. Accordingly, current United States (US) FDA guidance recommends a PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion (≥ 20 % of the absorbed drug) of the elimination of a parent drug or active metabolite [4].

The magnitude of the effect of mild, moderate, or severe HI on the PK of soticlestat was assessed based on model-based simulations of HI effect using in vitro enzyme phenotyping data and data from the human ADME study. The simulations suggested that in participants with mild, moderate, or severe HI, soticlestat AUC_{∞} is expected to be 1%, 23%, and 33% higher, respectively, than healthy participants with normal hepatic function; soticlestat C_{max} is expected to be 0%, 6%, and 7% higher, respectively, compared with healthy participants with normal hepatic function.

Based on model-based simulations, this study first evaluated the PK in participants with moderate HI (n=8) and healthy matched participants with normal hepatic function (n=12) and an interim PK analysis was conducted. The interim analysis indicated higher impact of moderate HI on soticlestat PK than the model predicted. For participants with moderate HI, soticlestat PK exposure increased to 214.93%, 316.47%, and 299.38% for C_{max}, AUC_{last}, and AUC_{∞}, respectively, when compared to the respective PK exposure in matched participants with normal hepatic function. As a result, this study will further evaluate the impact of mild HI on the PK of soticlestat. In addition, the Sponsor decides not to dose participants with severe HI. Soticlestat will not be recommended to use in subjects with severe HI.

4.3 Benefit/Risk Profile

The single dose of 300 mg soticlestat has been selected for this study as it is the recommended phase 3 dose [1]. In addition, doses up to 1350 mg were administered in healthy participants and were found to be safe and well tolerated.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, 12-lead ECG, vital signs, clinical laboratory tests, AE questioning, C-SSRS, and physical examinations) are adequate to protect the participant's safety and should detect all TEAEs.

There will be no direct health benefit for study participants from receipt of the study drugs. An indirect health benefit to the healthy participants enrolled in this study is the free medical tests received at screening and during the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable.

5.2 Study Objectives

5.2.1 Study Primary Objective

- To characterize the plasma PK of soticlestat following a single oral dose in participants with moderate or mild HI compared to matched healthy participants with normal hepatic function.

5.2.2 Study Secondary Objective

- To evaluate the safety and tolerability of soticlestat following a single oral dose in participants with moderate or mild HI as well as matched healthy participants with normal hepatic function.

[redacted]

[redacted]

5.3 Endpoints

5.3.1 Primary Endpoints

The following PK parameters in plasma will be analyzed for soticlestat:

- C_{max}
- AUC_{∞}
- AUC_{last}

5.3.2 Secondary Endpoints

- Incidence of TEAEs
- Incidence of clinically significant abnormal values for laboratory evaluations, vital signs, ECG parameters, and C-SSRS

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, open-label, study of oral soticlestat designed to assess the PK of single dose soticlestat [redacted] in participants with moderate or mild HI compared to matched healthy participants with normal hepatic function. At least 12 healthy participants (up to 24 participants) with normal hepatic function will be recruited to match the group mean of moderate and mild HI arms by age (mean ± 10 years), sex (± 2 per sex), and BMI (mean ± 10%). Eight (8) participants will also be enrolled in each HI arm of the study according to the following criteria:

- Arm 1: (N = 8): Moderate HI (Child-Pugh Class B [Score: ≥ 7 and ≤ 9]), 300 mg single dose
- Arm 2: (N = 8): Mild HI (Child-Pugh Class A [Score: ≥ 5 and ≤ 6]), 300 mg single dose
- Arm 3: (N = 12 - 24): Normal hepatic function, 300 mg single dose

The study will consist of a 28-day screening period (prior to dosing) and a 7-day confinement period (Day -1 to Day 7).

Two hepatic function assessments are required prior to Day 1 dosing for participants with HI. These 2 assessments should be obtained during the screening period and at least 48 hours apart. In the case, where a participant has an available historical Child-Pugh assessment score within 3 months prior to screening, 1 assessment can be conducted during the screening period. If the Child-Pugh scores from these 2 assessments indicate the same liver function category for the participant (ie, normal hepatic function, moderate HI, or mild HI), soticlestat can be administered as scheduled. If the results of the 2 assessments indicate different liver function categories, a third assessment must be conducted at least 24 hours after the second assessment. If the results of the 2 most recent assessments (the second and third) are in agreement with regard to the participant's liver function category, the participant may be enrolled and should receive the Day 1 dose within 48 hours of the third assessment. If the second and third measurements differ, the participant will not be eligible for the study.

The moderate HI arm (ie, Arm 1) will be conducted first, followed by 12 participants in the matched normal hepatic function arm (Arm 3). After all participants in moderate HI arm and the matching 12 participants in the matched normal hepatic function arm have completed the treatment period, an informal interim PK data analysis is planned and may additionally leverage historical control PK data in healthy participants to gain an initial estimate of the effect of moderate HI on the PK of soticlestat [redacted].

Following completion of enrolment of the mild HI arm, and in the instance any of the previously enrolled healthy participants cannot be used for matching purposes, up to an additional 12 participants may be enrolled for the matched normal hepatic function group (Arm 3) to ensure a minimum of 12 participants with normal hepatic function and matching the mean of the mild HI arm by age (mean ± 10 years), sex (± 2 per sex), and body mass index (BMI, mean ± 10%) are enrolled.

Participants will receive a single oral dose of 300 mg soticlestat as three 100 mg T4 tablets on Day 1 with approximately 240 mL water under fasting conditions. PK samples will be collected from Days 1 to 7, at predetermined time points (Section 3.0), to characterize the PK of soticlestat [redacted] in participants with moderate or mild HI compared to matched healthy participants with normal hepatic function (Section 3.0).

Participants will remain in the clinic throughout the study. Participants will be discharged from the clinic on Day 7 after the last PK sample collection and study procedures are completed. A safety follow-up contact of all participants (including those who terminate the study early) will occur 14 ± 2 days after the soticlestat dose to determine if any AEs have occurred since the CRU discharge.

6.2 Dose Escalation

Not applicable.

6.3 Stopping Rules

Not applicable.

6.4 Rationale for Study Design, Dose, and Endpoints

6.4.1 Rationale of Study Design

After entering the body, drugs are eliminated by excretion and/or metabolism. Although elimination can occur through a variety of routes, most drugs are cleared by metabolism in the liver and/or small intestine and/or by elimination of unchanged drug by the kidneys. Liver disease is associated with several pathophysiologic changes that may alter the PK of a drug. These include alterations in hepatic blood flow, changes in liver enzyme activity, decreased binding of drug to plasma proteins, and impaired biliary excretion [2, 3]. Accordingly the current United States (US) Food and Drug Administration (FDA) guidance recommends a PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion (ie, ≥ 20 % of the absorbed drug) of the elimination of a parent drug or active metabolite [4]. Urinary excretion is the major route for soticlestat elimination with 95% of the dose excreted in urine; however, urinary excretion of the parent drug is low (< 1% of the dose) indicating that metabolism is the near exclusive clearance pathway of soticlestat. TAK-935-G excreted in urine contributed to 86% of the dose suggesting that soticlestat was predominantly cleared by direct glucuronidation, thus the potential implications of HI on soticlestat's hepatic metabolism, should be evaluated.

This study will investigate the impact of impaired hepatic function on the plasma PK of soticlestat [redacted] and safety compared to matched healthy participants with normal hepatic function in order to provide dosing recommendations to clinicians for future treatments of soticlestat to patients with varying degrees of HI. An informal interim PK data analysis was performed following soticlestat administration in participants with moderate HI ($n=8$) and healthy matched participants with normal hepatic function, which has demonstrated higher than expected soticlestat exposure in participants with moderated HI than in healthy matched participants with normal hepatic function. The Sponsor has decided not to recommend soticlestat dosing in patients with severe HI, therefore participants with severe HI will not be enrolled in the current study. Instead, this study will enroll an arm of participants with mild HI in order to further investigate the impact of HI on soticlestat PK. Due to the variability of soticlestat PK and easier accessibility of healthy participants in comparison to participants with HI, an increased number of healthy participants will be enrolled.

The Child-Pugh classification will be used to categorize HI due to its widespread use and acceptance by regulatory agencies (including the FDA). It has been shown to correlate with hepatic (ie, metabolic) clearance for several compounds [4]. In the current study, participants with chronic, stable HI with features of cirrhosis due to any etiology will be enrolled using the

Child-Pugh scale. The scale employs five clinical measures of liver disease listed in Table 6.a. Each assessment is scored 1 - 3, with 3 indicating most severe derangement. Participants' scores of 5 to 6, 7 to 9, and 10 to 15 on this scale are classified as having mild, moderate, and severe HI, respectively.

Table 6.a Derivation of Child-Pugh Classification Score [1]

Parameter	1 point	2 points	3 points
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Prothrombin time (PT) (second prolonged) or International normalized ratio (INR) (ratio)	<4 <1.70	4 to 6 1.70 to 2.30	>6 >2.30
Ascites	Absent	Slight	Moderate or participants on medication to control ascites
Hepatic encephalopathy grade	None	Grade 1 or 2	Grade 3 or 4 or participant receiving medication(s) to prevent encephalopathy

[1] Adapted from U.S. Department of Health and Human Services. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (2003) [4].

Table 6.b Determination of Encephalopathy Grade [1]

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia
3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
4	Unrousable coma, no personality/behavior, decerebrate

[1] Adapted from U.S. Department of Health and Human Services. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (2003) [4].

6.4.2 Rationale for Dose

T4 tablets are immediate release tablets of 100 mg strength that will be utilized for phase 3 clinical studies and will be used in this study. The model simulation (SimCYP®) predicted increase in soticlestat exposure in participants with moderate or mild HI is within two-fold, therefore the dose of soticlestat selected for the HI study is 300 mg, the recommended phase 3 dose. The 300 mg dose is approximately 22% of the highest single dose of 1350 mg evaluated in healthy participants, and soticlestat exposure at 1350 mg was > 4-fold the exposure at 300 mg. In clinical studies, soticlestat administered as a single dose of up to 1350 mg was safe and well tolerated. As metabolism is the near exclusive clearance pathway of soticlestat in humans, the effect of moderate or mild HI on the exposure to soticlestat [redacted] will be characterized in this study

to establish scientifically guided dosing recommendations in these special patient populations. The PK of soticlestat [redacted] following oral administration of soticlestat in participants with moderate or mild HI using Child-Pugh scores will be compared to matched healthy participants with normal hepatic function.

6.4.3 Rationale for Endpoints

6.4.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of study.

6.4.3.2 Safety Endpoints

The key safety endpoints are typical for phase 1 studies and will be assessed through monitoring of AEs, vital signs, ECGs, laboratory assessments, C-SSRS, and physical examinations.

[redacted]

6.4.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is the blood collection for plasma concentrations of soticlestat [redacted], and is to be collected within the sampling windows.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of soticlestat for all participants with moderate HI, mild HI, and healthy participants with normal hepatic function (ie, Arms 1, 2, and 3) may not be modified.

After all participants in the moderate HI arm and 12 participants in the matched normal hepatic function arm have completed the treatment period, an informal interim PK data analysis is planned and may additionally leverage historical control PK data in healthy participants to gain an initial estimate of the effect of moderate HI on the PK of soticlestat [redacted]. Following completion of enrolment of the mild HI arm, and in the instance any of the previously enrolled healthy participants cannot be used for matching purposes, up to an additional 12 participants may be enrolled for the matched normal hepatic function group (Arm 3) to ensure a minimum of 12 participants with normal hepatic function and matching the mean of the mild HI arm by age (mean ± 10 years), sex (± 2 per sex), and body mass index (BMI, mean ± 10%) are enrolled.

If necessary, a participant may be discontinued for the reasons described in Section 7.5 and Section 7.6.

6.6 Study Beginning and End/Completion

6.6.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the ICF) of the first participant.

6.6.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0)

6.6.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the follow-up visit for the last participant in the study.

This time period may change in the event that the study is terminated early or the last participant is lost to follow-up.

6.6.4 Definition of Study Discontinuation

The clinical site(s) reserve(s) the right to terminate the study in the interest of participant welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.6.5 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for participants participating in the study.

- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

6.6.6 Criteria for Premature Termination or Suspension of a Site

6.6.6.1 Criteria for Premature Termination or Suspension

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

6.6.6.2 Procedures for Premature Termination or Suspension

In the event that the sponsor, an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or a regulatory authority elects to terminate or suspend the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational site(s) during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

7.1 Inclusion Criteria

7.1.1 Inclusion for Participants with Hepatic Impairment

Participants must fulfill the following inclusion criteria to be eligible for participation in the study (participants who do not qualify based on a reversible condition or mild intercurrent illness may be re-screened after the condition is resolved. Screening tests may be repeated if in the Investigator's opinion the test needs to be repeated):

1. Is an adult male or female participant aged ≥ 18 to < 75 years, at screening.
2. Has a BMI ≥ 18.0 and ≤ 40.0 kg/m^2, at screening. At least 50% of the participants will be required to be of BMI ≥ 18.0 and ≤ 35.0 kg/m^2, at screening.
3. Aside from HI, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, ECGs, and screening clinical laboratory profiles, as deemed by the Investigator or designee.
   - Supine BP is ≥ 80/40 mmHg (asymptomatic) and ≤ 150/95 mmHg, at screening;
   - Supine PR is ≥ 40 bpm and ≤ 99 bpm, at screening;
   - QTcF is ≤ 500 msec and ECG findings considered normal or not clinically significant by the Investigator or designee, at screening.
4. The participant must have had chronic HI for at least 3 months before screening, and the HI must be stable, ie, no significant changes in hepatic function in the 30 days preceding

screening (or since the last visit if within 6 months before screening) and treatment with stable doses of medication. Has a score on the Child-Pugh Class at screening as follows:

- (Arm 1) Moderate HI, Child-Pugh Class B: ≥ 7 and ≤ 9
- (Arm 2) Mild HI, Child-Pugh Class A: ≥ 5 and ≤ 6

5. Participants should not have renal dysfunction as demonstrated by a relatively adequate renal function (creatinine clearance ≥ 50 mL/min), at screening.

7.1.2 Inclusion for Healthy Participants

Participants must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Is an adult male or female participant aged ≥ 18 to < 75 years, at screening. Healthy participants will be matched to hepatic impaired participants in this study by sex (± 2 per sex) and by age (mean ± 10 years).
2. Has a BMI ≥ 18.0 and ≤ 40.0 kg/m^2, at screening. At least 50% of the participants will be required to be of BMI ≥ 18.0 and ≤ 35.0 kg/m^2, at screening. Healthy participants will be matched to hepatic impaired participants in this study by BMI (mean ± 10%).
3. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
   - Supine BP is ≥ 90/40 mmHg and ≤ 150/95 mmHg, at screening;
   - Supine PR is ≥ 40 bpm and ≤ 99 bpm, at screening;
   - QTcF is ≤ 450 msec (males) or ≤ 470 msec (females) and ECG findings considered normal or not clinically significant by the Investigator or designee, at screening;
   - Liver function tests including ALT, AST, ALP and total bilirubin ≤ the ULN at screening and check-in.
4. Participants should not have renal dysfunction as demonstrated by a relatively adequate renal function (creatinine clearance ≥ 60 mL/min), at screening.

7.1.3 Inclusion for Participants with Hepatic Impairment and Healthy Participants

Participants must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Understands the study procedures in the ICF, provides a signature/date in the ICF, and is willing and able to comply with the protocol.
2. Continuous non-smoker or moderate smoker (≤ 10 cigarettes/day or the equivalent) before screening. Participant must agree to consume no more than 5 cigarettes or equivalent/day from the 7 days prior check-in and until discharge from the CRU.
3. Female participants of childbearing potential and male participants agree to comply with any applicable contraceptive requirements of the protocol as detailed in Appendix D.

7.2 Exclusion Criteria

7.2.1 Exclusion for Participants with Hepatic Impairment

The participant must be excluded from participating in the study if the participant:

1. Has history or presence of clinically significant medical or psychiatric condition or disease (aside from HI) or presence of psychotic disorders such as psychosis, delusions, or schizophrenia in the opinion of the Investigator or designee.
2. Has a history of liver or other solid organ transplant.
3. Has history or presence of alcoholism and drug abuse within the past 6 months prior to dosing.
4. Positive result at screening for HIV. HBsAg positive participants are allowed to be enrolled if HBV DNA is below 1000 copies/mL in the plasma. Participants with moderate or mild HI who are positive for HCVAb can be enrolled but must not have detectable HCV RNA in the plasma.

7.2.2 Exclusion for Healthy Participants

The participant must be excluded from participating in the study if the participant:

1. Has history or presence of clinically significant medical or psychiatric condition or disease or presence of psychotic disorders such as psychosis, delusions, or schizophrenia in the opinion of the Investigator or designee.
2. Has history or presence of alcoholism and drug abuse within the past 2 years prior to dosing.
3. Positive results at screening for HIV, HBsAg, or HCV.

7.2.3 Exclusion for Participants with Hepatic Impairment and Healthy Participants

The participant must be excluded from participating in the study if the participant:

1. Has history of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
2. Has history or presence of clinically significant hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
3. Has positive results for the urine or saliva drug screen at screening or check-in, unless the positive drug screen is due to prescription drug use that is approved by the Investigator (cannabinoids can be used for medicinal use at the discretion of the Investigator).
4. Is a female with a positive pregnancy test or who is lactating.
5. Has positive results for urine or breath alcohol screen at screening or check-in.
6. Is unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 7.3 (Excluded Medications, Supplements, Dietary Products) for the prohibited time period.

7. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing.
8. Has made a donation of blood or had significant blood loss within 56 days prior to dosing.
9. Has made a plasma donation within 7 days prior to dosing.
10. Participated in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.
11. Any positive responses on the C-SSRS or has a risk of suicide according to the Investigator's judgment based on the assessment of the C-SSRS at screening or check-in or has made a suicide attempt in the previous 12 months prior to dosing.

7.3 Excluded Medications, Supplements, Dietary Products

Healthy participants will be restricted of using any prescription medications/products and any over-the-counter, nonprescription preparations (including herbal products, natural or herbal supplements) from at least 14 days before dosing and throughout the study. However, healthy participants that are on stable medication for at least 30 days prior to dosing may be enrolled upon approval by the Investigator (or designee) and Sponsor.

Participants with HI who are taking medications to treat manifestations of hepatic disease or medications needed to treat for stable diseases (e.g., diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and beta-blockers) will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor. For hepatic disease related medical conditions, participants must be on a stable dose (steady dose, drug, and regimen) for at least 30 days and/or for non-hepatic disease related medical conditions for 14 days before dosing and able to withhold the use for at least 4 hours postdose. Phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; H2-receptor antagonists (except cimetidine); or multivitamins containing iron or zinc must be withheld at least 8 hours before dosing and at least 4 hours postdose.

If a participant with HI is prescribed prohibited medication, upon discussion between the sponsor and the Investigator, the Investigator may substitute the previously prescribed medication to an allowed one for the purpose of this study.

For all participants, any drugs known to be strong inhibitors or inducers of CYP3A, UGT1A9 or UGT2B4, including St. John's Wort, will be restricted for 14 days or 28 days, respectively, before dosing and throughout the study. Use of moderate and weak inhibitors or moderate and weak inducers may be deemed acceptable following consultation with the sponsor and the Investigator or designee. Appropriate sources (e.g., Flockhart Table™) will be consulted to confirm lack of PK/PD interaction with study drug. Cannabinoids can be used for medicinal use at the discretion of the Investigator.

For all participants, following dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee.

Any medication (including over-the-counter) that would significantly alter creatinine clearance, which, by the determination of the Investigator, might interfere with the study (e.g., cimetidine) must be discontinued at least 2 weeks prior to dosing and throughout the study.

All medications taken by participants during the course of the study will be recorded.

Concurrent medication during the course of the study including both prescription and non-prescription drugs may be permitted based on the timing of study drug administration and its pharmacology, but must first be discussed with the Investigator or designee and sponsor prior to dosing, unless appropriate medical care necessitates that therapy should begin before the Investigator or designee and sponsor can be consulted.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case by case basis whether the participant may continue participation in the study based on the time the drugs were administered and their pharmacology.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and First Dosing (Days -28 to Predose [Day 1])	After Dosing (Day 1) to Discharge (Day 7)
Alcohol	Prohibited from 48 hours prior to dosing	Prohibited from dosing until discharge from CRU completed.
Xanthine and/or caffeine	Prohibited from 24 hours prior to dosing [a]	Prohibited from dosing until discharge from CRU completed.[a]
Medications	See Section 7.3	See Sections 7.3
Food substance		
Grapefruit/Seville orange	Prohibited from 14 days prior to dosing	Prohibited from dosing until discharge from CRU completed.
Nicotine and analogous derivatives	≤ 5 cigarettes/day 7 days prior to dosing	≤ 5 cigarettes/day until discharge from CRU completed.

(a) small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after dosing, but will be allowed ad libitum at all other times, when dosing occurs at the CRU. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Participants will fast overnight for at least 10 hours prior to dosing. Participants will continue the fast for at least 4 hours postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, participants will be required to fast from all food and drink except water between meals and snacks.

7.4.2 Activity

All participants will remain seated for the first 4 hours following dosing, except when they are supine or semi-reclined for study procedures. Participants will then resume normal activity.

However, should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side. During the first 4 hours postdose, participants may be allowed to rise for brief periods under supervision (e.g., in order to use the toilet facilities).

Participants will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

Participants must not consume more than 5 cigarettes or equivalent/day from the 7 days prior to check-in and until discharge from the CRU. Depending on the CRU rules and regulations, participants may be prohibited from smoking during their confinement or during portions of their confinement.

7.5 Criteria for Discontinuation or Withdrawal of a Participant

The primary reason for discontinuation or withdrawal of the participant from the study or study drug should be recorded in the case report form (CRF) using the following categories.

1. Pretreatment event (PTE) or AE: The participant has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the participant's health or the participant is unwilling to continue because of the PTE or AE.

   Liver Function Test (LFT) Abnormalities

   Appropriate clinical follow-up will be conducted (including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status, see Section 9.2.9.1), if the following circumstances occur at any time following study drug treatment:

   – ALT or AST >8x ULN, or
   – ALT or AST >5x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

   QTcF interval:

   Appropriate clinical follow-up will be conducted if a QTcF interval >500 msec and/or an increase from baseline > 60 msec is detected by ECG and confirmed with a repeat ECG at any time following study drug treatment. Appropriate clinical follow-up includes a repeat ECG.

2. Significant protocol deviation: The discovery post-enrollment that the participants failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the participant's health.
3. Lost to follow-up: Attempts to contact the participants were unsuccessful. Attempts to contact the participant must be documented in the participant's source documents.
4. Voluntary withdrawal: The participants (or participant's legally acceptable representative) wish to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category). If a participant chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for participant withdrawal in the CRF.
5. Study termination: The Sponsor, IRB/ IEC, or regulatory agency terminates the study.
6. Pregnancy: as described in Appendix D.
7. Participants may be withdrawn from the study by the Investigator or designee for the following reasons:
   - Difficulties in blood collection.
   - Positive urine drug or alcohol test.

Other: The specific reasons for discontinuation should be entered into the CRF including unavoidable circumstances such as the COVID-19 pandemic. Participants may be withdrawn from the study at any time at the discretion of the Investigator or sponsor for safety reasons which should be entered into the CRF.

7.6 Procedures for Discontinuation or Withdrawal of a Participant

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 7.5. In addition, a participant may discontinue his or her participation without giving a reason at any time during the study. Should a participant's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.7 Participant Replacement

Replacement of discontinued or withdrawn participants due to any reason will be assessed on a case by case basis by the sponsor and Investigator. Any participant who is not PK evaluable including those experiencing emesis within 8 hours post dose may be replaced at the discretion of the Investigators in consultation with the sponsor to ensure 8 PK-evaluable participants in each

arm of participants with HI and 12-24 PK-evaluable participants in matched participants with normal hepatic function complete.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Investigational Medicinal Product

Product Name:	Soticlestat (TAK-935)
Strength:	100 mg
Dose:	300 mg, 3 x 100mg
Dosage Form/Formulation:	T4 immediate-release tablet
Dosing regimen:	Single dose
Route of Administration:	Oral

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drug supplied will be recorded in the final report. Study drugs will be stored according to the product labels provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.3 Clinical Study Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage

Not applicable.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused soticlestat will be retained by Celerion/clinical sites, as applicable,

returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the participants in non-technical terms. Participants will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Participants will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Identification Numbers

Each participant will be assigned a unique identification number upon screening. Participants who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number.

If replacement participants are used, the replacement participant number will be 100 more than the original participant's identification number (eg, Participant No. 101 will be assigned to the replacement of Participant No. 1).

9.1.1.2 Study Drug Assignment

All participants will receive the treatments as detailed in Section 9.2.8.

9.1.2 Inclusion and Exclusion

Please refer to Section 7.1 and Section 7.2.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, history of tobacco use, and Child-Pugh classification will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.3. All medications taken by participants during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional

evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to participant safety.

For this study, collection of blood for plasma soticlestat [redacted] PK is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Full Physical Examination

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of temperature, respiratory rate, BP, and PR will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and pulse rate measurements will be performed with participants in a supine position (after resting in a supine position for at least 5 minutes), except when they are semi-reclined because of study procedures and/or AEs (e.g. nausea, dizziness) or if deemed necessary by the Investigator or designee.

Vital signs will be measured within 24 hours prior to dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with participants in a supine position (after resting in supine position for at least 5 minutes). All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within 24 hours prior to dosing for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Study Drug Administration

Soticlestat will be provided as described in Section 8.1.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each participant, as appropriate.

Study drug will be administered with approximately 240 mL of water.

Participants will be instructed not to crush, split, or chew the tablets.

The exact clock time of dosing will be recorded.

Treatment will be administered as follows:

Soticlestat 300 mg (3 x 100 mg T4 tablets) at Hour 0 on Day 1.

9.2.7 C-SSRS

Suicidal ideation will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures (Section 3.0). Two versions of the C-SSRS will be used in this study: the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS. Any suicidal ideation or suicidal behavior during the trial periods detected by the C-SSRS will be recorded as an AE. The Investigator will ensure that any suicidal ideation or behavior is medically addressed, including assessment and treatment by qualified medical personnel. When possible, it is highly recommended that assessments will be conducted by the same rater for consistency.

9.2.8 AE Monitoring

Participants will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10.0.

9.2.9 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Coagulation

Coagulation test will consist of the following tests:

Activated partial thromboplastin time	PT/ INR

Chemistry

Serum chemistry tests will be performed in the fasted state after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Amylase	Sodium
Lipase	Potassium
Blood Urea Nitrogen	Chloride
Bilirubin (total and direct)	Glucose
ALP	Creatinine *
AST	Magnesium
ALT	
AGP	
Albumin	

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault equation.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

9.2.9.1.1 Other

HIV test	Urine/saliva drug screen
HBsAg *(if antibody positive, confirm DNA is below 1000 copies/mL in participants with HI)*	Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone)
HCV *(if antibody positive, confirm RNA negative in participants with HI)*	Amphetamines
Urine/breath alcohol screen	Barbiturates
Serum pregnancy test (for females only)	Benzodiazepines
FSH (for females only)	Cocaine
	Cannabinoids

9.3 PK Samples

Samples for assessment of soticlestat [redacted] will be collected as delineated in Table 9.a.

Instructions for sample collection, processing, and shipping will be provided in separate documents.

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

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK (Soticlestat [redacted])	Blood	Plasma	Plasma sample for PK analysis	Mandatory
[redacted]	Blood	Plasma	[redacted]	Mandatory

9.3.1 PK Measurements

Samples from all participants will be assayed even if the participants do not complete the study. Samples for determination of plasma soticlestat [redacted] will be analyzed using validated bioanalytical methods.

Pharmacokinetic parameters of soticlestat [redacted] will be calculated from the individual concentration-time profiles from all evaluable participants using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The fraction of unbound soticlestat will be determined.

9.3.1.1 Plasma for PK Measurements

The following PK parameters will be calculated from plasma concentrations of sotisclestat [redacted] unless otherwise specified:

AUC_{last}: The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.

AUC_{∞}: The area under the concentration-time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_{last} plus the ratio of the last measurable blood concentration to the elimination rate constant.

[redacted]

C_{max}: Maximum observed concentration.

[redacted]

No value for [redacted] AUC_{∞}, [redacted] will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for participants with detectable concentrations at 2 or fewer consecutive time points.

Individual and mean plasma concentration-curves (both linear and log-linear) will be included in the final report.

Additional PK parameters may be estimated as appropriate.

9.3.2 Biomarker Measurements

Not applicable.

9.3.3 PGx Measurements

Not applicable.

9.3.4 Confinement

Participants will be restricted and confined to the CRU on Day -1, at the time indicated by the CRU, until after the 144-hour blood draw and/or study procedures (Day 7) as outlined in the Schedule of Study Procedures (Section 3.0). Participants may be admitted to the CRU earlier for COVID-19 procedures not related to the study protocol.

At all times, a participant may be required to remain at the CRU for longer for safety reasons at the discretion of the Investigator or designee.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation participant who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

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

A TEAE is defined as any untoward medical occurrence in a clinical investigation participant that occurs following administration of the investigational study drug.

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the participant experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a participant has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, Investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a participant has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the participant experiences a worsening or complication of an AE after the administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the participant experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study participant, at a dose above that which is assigned to that individual participant according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the participant should be treated symptomatically.

10.1.1 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the 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.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.

6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
COVID-19-related disease COVID-19 pneumonia	Spontaneous abortion / stillbirth and fetal death

Abbreviations: COVID-19 = Coronavirus disease 2019

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

There are no AEs of Special Interest for this study.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.

- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the participant died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

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

10.2.8 Collection and Reporting of AEs, SAEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the participant signs the informed consent. Routine collection of AEs will continue until the follow-up phone call on Day 14 ± 2 days after the soticlestat dose. For participants who discontinue prior to the administration of study medication, AEs will be followed until the participant discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Participants may report AEs occurring at any other time during the study. Participants

experiencing an SAE prior to the exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

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

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

A Takeda SAE form must be completed, in English and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Participant identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Appendix 14.1.1.

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

Reporting of SAEs that begin before administration of investigational product will follow the same procedure for SAEs occurring on treatment.

10.2.8.3.1 SAE Follow-Up

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

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

10.2.8.4 Reporting Special Interest AEs

Not Applicable.

10.2.8.5 Reporting of Abnormal LFTs

Healthy Participants Only

If a participant is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

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, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The Investigator must contact the Medical Monitor for discussion of the relevant participant details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 10.0 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

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

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be

sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 PK Set

All participants who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

11.1.1.2 Safety Set

All participants who received the dose of soticlestat will be included in the safety evaluations.

11.1.1.3 PD Set

Not applicable.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, sex, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

Statistical analysis of PK data will be based on the PK analysis set.

Descriptive statistics will be used to summarize concentrations of soticlestat and PK parameters according to hepatic function group (normal hepatic function, moderate and mild HI). An ANOVA will be performed on the ln-transformed C_{max}, AUC_{last}, and AUC_{∞} for soticlestat to compare each HI group with the normal hepatic function group, and 90% CIs for the ratio of geometric means from each HI group versus normal function group will be provided. The addition of other factors and covariates such as age, sex, and BMI on the relationship between soticlestat PK parameters and level of HI may also be investigated.

Descriptive statistics will be used to summarize concentrations [redacted] and PK parameters according to hepatic function group (normal hepatic function and moderate and mild HI).

The fraction of unbound soticlestat will be determined.

11.1.4 PD Analysis

Not applicable.

11.1.5 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by participant.

TEAEs will be tabulated. The remaining quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.5.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by group for the number of participants reporting the TEAE and the number of TEAEs reported. A by-participant AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided. AEs that occur before administration of study drug will be included in listings but will not be summarized.

11.1.5.2 Clinical Laboratory

Clinical laboratory results will be summarized by group and point of time of collection and a shift table describing out of normal range shifts will be provided.

MAV criteria for safety laboratory assessments will be defined in the SAP.

11.1.5.3 Vital Signs

Vital signs assessments will be summarized by group and point of time of collection and a shift table describing out of normal range shifts will be provided.

MAV criteria for vital signs will be defined in the SAP.

11.1.5.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs and C-SSRS results will be summarized by group and point of time of collection and a shift table describing out of normal range shifts will be provided.

MAV criteria for ECGs will be defined in the SAP.

Medical history and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be listed by participant.

11.2 Interim Analysis and Criteria for Early Termination

After all participants in the moderate HI arm and 12 participants in the matched normal hepatic function arm are enrolled, an informal interim PK data analysis is planned and may additionally leverage historical control PK data in healthy participants to gain an initial estimate of the effect of moderate HI on the PK of soticlestat [redacted].

11.3 Determination of Sample Size

The planned sample size of 8 participants in each HI arm is not based on power calculations and is considered adequate to provide a descriptive characterization of the PK of soticlestat [redacted] in participants with moderate or mild HI compared to healthy participants with normal hepatic function.

Any participant who is not PK evaluable including those experiencing emesis within 8 hours post dose may be replaced at the discretion of the Investigators in consultation with the sponsor to ensure 8 PK-evaluable participants in each arm of participants with HI and 12-24 PK-evaluable participants in matched participants with normal hepatic function complete.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study sites will be made periodically during the study to ensure that all aspects of the protocol are followed. Detailed information for monitoring visits to be conducted in this study will be documented in a Clinical Research Associate Monitoring Plan and followed during the study. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee contract research organization and by the IRB or IEC.

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

12.2 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.

For COVID-19-related protocol deviations, the specific protocol deviation, the reason for the deviation, and the relationship to COVID-19 should be documented using CRU standard processes.

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.

Detailed information for medical and safety monitoring to be conducted in this study will be documented in a Medical Monitoring Plan and followed during the study.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

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 FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

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 on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 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 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, a copy of 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 (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). 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. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the 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 IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Participant incentives should not exert undue influence for participation. Payments to participant must be approved by the IRB or IEC and Sponsor.

13.2 Participant Information, Informed Consent, and Participant Authorization

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

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the participant authorization form. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be written in a language fully comprehensible to the prospective participant. It is the responsibility of the Investigator to explain the detailed elements of the ICF, participant

authorization form (if applicable), and participant information sheet (if applicable) to the participant. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the 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.

The participant, or the participant's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the participant, or the participant's legally acceptable representative, determines he or she will participate in the study, then the ICF and participant authorization form (if applicable) must be signed and dated by the participant, or the participant's legally acceptable representative, at the time of consent and prior to the participant 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 blue or black ballpoint ink. The Investigator must also sign and date the ICF and participant authorization (if applicable) at the time of consent and prior to participant entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, participant authorization form (if applicable), and participant information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed ICF, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

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

13.3 Participant Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the participant's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study

participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process (see Section 13.2).

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

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

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

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

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

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting trial information. Once participants receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established participant screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the Sponsor.

Any Investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

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

13.5 Insurance and Compensation for Injury

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.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. [redacted]

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

[redacted]

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- International Council on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

[redacted]

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- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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

[redacted]

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

[redacted]

µg	Microgram
24HC	24*S*-hydroxycholesterol
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AGP	Alpha-1-acid glycoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{∞}	The area under the concentration-time curve, from time 0 to infinity
AUC_{last}	The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CDD	CDKL5 deficiency disorder
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CH24H	cholesterol 24*S* hydroxylase
CI	Confidence interval

[redacted]

Cm	Centimeter
C_{max}	Maximum observed concentration
COVID-19	Coronavirus Disease-2019
CRF	Case report form
CRU	Clinical Research Unit
CSR	Clinical study report
CYP	Cytochrome P450
DEE	Developmental and Epileptic Encephalopathies
dL	Deciliter
DNA	Deoxyribonucleic acid

DS	Dravet Syndrome
Dup15q	15q11-q13 duplication syndrome
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
h	Hour(s)
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HCVAb	Hepatitis C virus antibodies
HI	hepatic impairment
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
kg	Kilogram
L	Liter
LFT	Liver function test
LGS	Lennox Gastaut Syndrome
ln	Natural log
m^2	Meters squared
MAV	Markedly abnormal values
µg	Microgram
µmol	Micromole
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
[redacted]	
msec	Millisecond
N	Number
OATP	organic-anion-transporting polypeptide
PD	Pharmacodynamic(s)

PK	Pharmacokinetic(s)
PR	Pulse rate
PT	Prothrombin time
PTE	Pretreatment event
QD	Daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
$t_{½z}$	Terminal disposition phase half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time of first occurrence of C_{max}
UGT	Uridine 5' diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
USA	United States of America
[redacted]	
WHO	World Health Organization

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 CRFs (Electronic and Paper)

Completed CRFs are required for each participant who signs an informed consent.

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs must be completed in English. Data are transcribed directly onto CRFs.

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.

Corrections 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 additionally be included.

The principal Investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the Investigator with use of change and modification records of the CRFs. The principal Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the participant's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs 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.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, participant authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of CRFs, 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 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The Investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

1. TAK-935. Takeda Pharmaceutical Company Ltd. Global Investigator's Brochure. Edition 7, 31 January 2022; plus Addendum 1, 03 February 2022, for Edition 7, 31 January 2022.
2. Rodighiero V. Effects of liver disease on pharmacokinetics. An update. Clin Pharmacokinet 1999;37(5):399-431.
3. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. European Journal of Clinical Pharmacology 2008;64(12):1147-61.
4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. May 2003.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential participants, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. 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.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each particiant who participates in the study, and document the date of consent in the participant's medical chart. Valid informed consent 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.

10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Participant Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the participant's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of participants involved in the study.
7. A description of the participant's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the participant may receive.
11. A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.
12. 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.
13. 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.
14. 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 a written ICF, the participant or the participant's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the participant for participating in the study.
17. The anticipated expenses, if any, to the participant for participating in the study.
18. 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.

19. 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, and 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.
20. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
21. 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.
22. The foreseeable circumstances or reasons under which the participant's participation in the study may be terminated.
23. A written 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:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer 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;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) 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
    e) that the participant's identity will remain confidential in the event that study results are published.
24. Female participants of childbearing potential (eg, nonsterilized, premenopausal female participants) who are sexually active must use highly effective/effective contraception (as

defined in the informed consent) from signing the informed consent, throughout the duration of the study, and 30 days after dosing of study drug. Regular pregnancy tests will be performed throughout the study for all female participants.

25. Male participants must use effective contraception (as defined in the informed consent) from signing the informed consent, throughout the duration of the study and for 90 days after dosing of study drug.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

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

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

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

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Participants

From signing of informed consent, throughout the duration of the study, and for 90 days after dosing of study drug, nonsterilized* male participants who are sexually active with a female partner of childbearing potential** must agree to use a condom with spermicide. In addition, they must be advised not to donate sperm during this period.

Female Participants and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 30 days after dosing of study drug, female participants of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list below).

In addition they must be advised not to donate ova during this period.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to dosing. A male who has been vasectomized less than 4 months prior to study dosing must follow the same restrictions as a non-vasectomized male).

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

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, acceptable methods of contraception are:
    - Non-Hormonal Methods:
        - IUD
        - Bilateral tubal occlusion;
        - bilateral salpingectomy;

- hysterectomy;
- bilateral oophorectomy;
- Vasectomised partner (provided that partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical assessment of the surgical success).

- Hormonal Methods:

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

  - oral.
  - Intravaginal (eg, ring).
  - transdermal.

Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 6 months prior to the dose of study drug OR combined with a barrier method (male condom with or without spermicide) if shorter till she has been on contraceptive for 6 months;

- oral.
- Injectable.
- Implantable.

2. Effective methods of contraception (there may be a higher than 1% failure rate). In this study, where medications and devices containing hormones are included, acceptable methods of contraception are:

   – Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom)

3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.

4. Participants will be provided with information on highly effective/effective methods of contraception as part of the participant informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
5. During the course of the study, regular human chorionic gonadotropin (hCG) pregnancy tests will be performed only for all females and all participants (male and female) will receive continued guidance with respect to the avoidance of pregnancy, ova donation, and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) assessment of participant compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
6. In addition to a negative serum hCG pregnancy test at Screening, female participants of childbearing potential must also have confirmed menses in the month before dosing (no delayed menses; with the exception of female participants using a protocol acceptable contraception method that has a known side effect of delayed or irregular menses). In addition, participants must also have a negative serum hCG pregnancy test prior to receiving the dose of investigational drug as close as possible and prior to the dose of investigational drug, preferably on the same day.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- assessment of participant compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

Pregnancy

If any participant is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male participant during the study or for 90 days after dosing, should also be recorded following authorization from the participant's partner.

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

All pregnancies, including female partners of male participants, in participants on active study drug (including comparator, if applicable) 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.

Appendix E Summary of Changes from Previous Version

The protocol is amended following informal interim PK analysis in participants with moderate HI and matching healthy subjects with normal hepatic function. The interim analysis indicated higher impact of moderate HI on soticlestat PK than predicted based on model-based stimulations. The Sponsor decided to remove the participants with severe HI from the study because soticlestat will not be recommended to use in subjects with severe HI. The study protocol is amended to evaluate the impact of mild HI on the PK of soticlestat.

A summary of changes incorporated into Amendment 1 is provided in the table below.

Summary of Changes(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
The protocol is update to replace participants with severe HI in Arm 2 with participants with mild HI.	Title Page Section 1.0 (Study Summary) Section 3.0 (Schedule of Study Procedures) Section 4.2 (Rationale for the Proposed Study) Section 5.2.1 (Study Primary Objective) Section 5.2.2 (Study Secondary Objective) Section 5.2.3 (Study Exploratory Objective) Section 6.1 (Study Design) Section 6.4.1 (Rational of Study Design) Section 6.4.2 (Rationale for Dose) Section 6.5 (Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters) Section 7.1.1 (Inclusion for Participants with Hepatic Impairment) Section 7.2.1 (Exclusion for Participants with Hepatic Impairment) Section 11.1.3 (PK Analysis) Section 11.3 (Determination of Sample Size)
Participants with mild HI enrolled in Arm 2 of the study will receive a single 300 mg dose of soticlestat. The protocol is updated to the remove the allowance to modify the dose of soticlestat for	Section 1.0 (Study Summary) Section 6.1 (Study Design) Section 6.5 (Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters)

participants in Arm 2 following interim PK analysis.	Section 8.1 (Clinical Study Drug) Section 9.2.6 (Study Drug Administration) Section 11.2 (Interim Analysis and Criteria for Early Termination)
Rationale for the amendment and change in HI population was added.	Section 4.2 (Rationale for the Proposed Study) Section 6.4.1 (Rational of Study Design)
The protocol is updated to include data from the most current IB version: "TAK-935. Takeda Pharmaceutical Company Ltd. Global Investigator's Brochure. Addendum 1, 03 February 2022, for Edition 7, 31 January 2022"	Section 4.1.1 (Soticlestat (TAK-035)) Section 16.0 (References)
The protocol is updated to correct units used for creatinine clearance listed in the inclusion criteria section as indicated in protocol clarification letter dated 03 November 2021. Creatinine clearance units were incorrectly presented as mL/min/1.73m^2 and are changed to mL/min since Cockcroft-Gault equation will be used for creatinine clearance calculation.	Section 1 (Study Summary) Section 7.1.1 (Inclusion for Participants with Hepatic Impairment) Section 7.1.2 (Inclusion for Healthy Participants)
The protocol is updated to increase the number of planned clinical sites from up to 3 sites to up to 7 sites.	Section 1 (Study Summary)
The protocol is updated to include new details for future biomedical research on residual plasma PK samples.	Section 6.4.4 (Future Biomedical Research)
The protocol is updated to clarify that HBV DNA will be measured in participants with HI with positive HBsAg results. HCV RNA will be measured in participants with HI with positive HCV antibody results	Section 9.2.9.1.1 (Other)

Typographical and grammatical corrections, as well as formatting changes, were made throughout the protocol.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	11-Apr-2022 20:35 UTC
	Clinical Approval	11-Apr-2022 21:56 UTC
	Biostatistics Approval	11-Apr-2022 23:36 UTC