Clinical Study Protocol

NCT Number: NCT05284760

Title: A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Bioequivalence of Soticlestat Oral Tablet Formulations and the Effect of Food and Tablet Crushing on the Pharmacokinetics of Soticlestat in Healthy Adult Participants

Study Number: TAK-935-1014

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

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Bioequivalence of Soticlestat Oral Tablet Formulations and the Effect of Food and Tablet Crushing on the Pharmacokinetics of Soticlestat in Healthy Adult Participants

Study Identifier: TAK-935-1014

Compound: Soticlestat (TAK-935)

Sponsor: Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington, MA 02421

IND No.: 133,627

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18 February 2022	Initial Version		United States
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Development Center Americas, Inc. (TDCA) 95 Hayden Avenue Lexington, MA 02421 Telephone: +1 (617) 679-7000	Soticlestat (TAK-935)
Study Identifier: TAK-935-1014	**Phase:** 1
Protocol Title: A Phase, 1 Open-Label, Randomized, Crossover Study to Evaluate the Bioequivalence of Soticlestat Oral Tablet Formulations and the Effect of Food and Tablet Crushing on the Pharmacokinetics of Soticlestat in Healthy Adult Participants	

Study Design:

This is a 2-part, open-label study conducted in healthy adult participants. Part A will evaluate the bioequivalence (BE) of 3 different soticlestat oral tablet formulations. Part B will evaluate the effect of food and tablet crushing on soticlestat pharmacokinetics (PK).

Each part will be conducted independently as a randomized, 3-period, crossover design. Study schematics of the study design are shown in Table 2.a, Table 2.b, Table 2.c, and Table 2.d. A schedule of assessments is shown in Schedule of Study Procedures (Section 3.0).

The two study parts may be conducted concurrently. Participants can only participate in one study part.

Part A:

Participants will be screened within 4 weeks (28 days) prior to the first dosing (Day -28 to first dosing on Day 1 of Period 1). Upon completion of screening, qualified participants will be admitted to the study site on Day -1 of Period 1 and will remain confined until completion of study procedures on Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

In each period, on Day 1, participants will receive a single oral dose of 300 mg soticlestat administered as T4 tablets (Treatment A), T3 mini-tablets (Treatment B), or commercial tablets (Treatment C), in a 3-way crossover fashion. Blood samples for the PK of soticlestat [redacted] will be collected at scheduled time points from predose through 96 hours postdose. There will be a washout period of exactly 4 days between each soticlestat doses.

Safety and tolerability will be assessed throughout the study by treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, physical examinations, Columbia-Suicide Severity Rating Scale (C-SSRS), 12-lead electrocardiograms (ECGs), and vital signs.

After discharge, the Clinical Research Unit (CRU) will contact all participants (including participants who terminate the study early) 14 (±3) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any adverse events (AEs) have occurred and/or any concomitant medications were taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

Part B:

Participants will be screened within 4 weeks (28 days) prior to the first dosing (Day -28 to first dosing on Day 1 of Period 1). Upon completion of screening, qualified participants will be admitted to the study site on Day -1 of Period 1 and will remain confined until completion of study procedures on Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

In each period, on Day 1, participants will receive a single oral dose of 300 mg soticlestat administered as intact T4 tablets under fasting conditions (Treatment D), intact T4 tablets fed conditions (Treatment E), or as crushed T4 tablets mixed with applesauce under fasting conditions (Treatment F), in a 3-way crossover fashion. Blood samples for the PK of soticlestat [redacted] will be collected at scheduled time points from predose through 96 hours postdose. There will be a washout period of exactly 4 days between each soticlestat doses.

Safety and tolerability will be assessed throughout the study by TEAEs, clinical laboratory evaluations, physical examinations, C-SSRS, 12-lead ECGs, and vital signs.

After discharge, the CRU will contact all participants (including participants who terminate the study early) 14 (±3) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any AEs have occurred and/or any concomitant medications were taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

Study Primary Objectives:

Part A:

- To assess the BE of 300 mg soticlestat administered as T3 mini-tablets (Treatment B) compared to 300 mg soticlestat administered as T4 tablets (Treatment A).
- To assess the BE of 300 mg soticlestat administered as commercial tablets (Treatment C) compared to 300 mg soticlestat administered as T4 tablets (Treatment A).

Part B:

- To assess the effect of food on the bioavailability (BA) of 300 mg soticlestat administered as T4 tablets under fed condition (Treatment E) compared to fasting condition (Treatment D).
- To assess the effect of tablet crushing on the PK of 300 mg soticlestat administered as T4 tablets crushed and mixed with applesauce (Treatment F) compared to whole T4 tablets (Treatment D).

Study Secondary Objective:

- To evaluate the safety and tolerability of soticlestat following single oral dose of 300 mg soticlestat in Treatments A, B, C, D, E, and F.

Study Exploratory Objectives:

[redacted]

Study Participant Population: Healthy male and female participants aged 18 to 55 years inclusive, at screening. Body Mass Index (BMI) 18.0-32.0 kg/m^2, inclusive, at screening

Planned Number of Participants:	**Planned Number of Sites:**
96 participants will be enrolled (72 participants in Part A and 24 participants in Part B)	1
Dose Levels: Treatment A, Treatment D, Treatment E, and Treatment F: 300 mg (3 x 100 mg strength T4 tablets) Treatment B: 300 mg (15 x 20 mg strength T3 mini-tablets). Treatment C: 300 mg (1 x 300 mg strength commercial tablet)	**Route of Administration:** Oral
Duration of Treatment: Single-dose of soticlestat on Day 1 of each period.	**Planned Study Duration:** Approximately 51 days including screening period and follow-up.

Criteria for Inclusion:

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

1. Healthy, adult, male or female of non-childbearing potential (Appendix D), 18 to 55 years of age, inclusive, at screening.
2. Male agrees to comply with any applicable contraceptive requirements of the protocol as detailed in Appendix D.
3. Body mass index (BMI) ≥ 18.0 and ≤ 32.0 kg/m^2 at screening.
4. Continuous non-smoker who has not used nicotine-containing products for at least 90 days prior to the first dosing.
5. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, and ECGs, as deemed by the Investigator or designee.
   - Supine blood pressure is ≥ 90/40 mmHg and ≤ 140/90 mmHg at screening;
   - Supine heart rate is ≥ 45 bpm and ≤ 100 bpm at screening;
   - QT interval corrected for pulse rate using Fridericia's formula (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;
   - Estimated creatinine clearance ≥ 80 mL/min at screening.
   - Liver function tests (LFT) including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 1.5 X the upper limit of normal (ULN) at screening and check-in.
6. Able to swallow multiple tablets.
7. Understands the study procedures in the Informed Consent Form (ICF), and be willing and able to comply with the protocol.

Criteria for Exclusion:

Participants must not be enrolled in the study if they meet any of the following criteria prior to the first dosing:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of gastritis, gastrointestinal (GI) tract, gastric bypass surgery, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.
4. History or presence of any of the following, deemed clinically significant by the Investigator or designee:
   - GI disorder (eg peptic ulcer disease, gastroesophageal reflux disease, impaction, chronic constipation, inflammatory bowel disease, ischemic colitis, vascular intestinal atherosclerosis, previous bowel resection, bowel obstruction, bariatric surgery, cholecystitis, intestinal ulceration or inflammation);
   - GI bleeding or perforation;
   - Recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding).
5. History or presence of cataracts.
6. History or presence of other clinically significant vision disturbances as judged by the Investigator or designee.
7. History or presence of epilepsy, seizure, or convulsion, tremor or related symptoms that are deemed clinically significant by the Investigator or designee.
8. 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.
9. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
10. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.
11. Any positive responses on the C-SSRS that in the clinical judgement of the Investigator has a risk of suicide or has made a suicide attempt in the previous 12 months prior to the first dosing.
12. Female participant of childbearing potential.

13. Female participant with a positive pregnancy test at screening or check-in or who is lactating.
14. Positive urine drug or alcohol results at screening or check-in.
15. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
16. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing. Thyroid hormone replacement medication may be permitted if the participant has been on the same stable dose for the immediate 3 months prior to the first dosing.
    - Any drugs known to be significant inducers of cytochrome P450 (CYP) 3A, CYP2C19, Uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9 or UGT2B4 enzymes and/or P-glycoprotein (P-gp), including St. John's Wort, within 28 days prior to the first dosing. Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drug.
17. History of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to the following: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz] per day).
18. Consumes excessive amounts, defined as greater than 4 servings (1 serving is approximately equivalent to 120 mg of caffeine), of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
19. 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 the first dosing and throughout the study.
20. Donation of blood or significant blood loss within 56 days prior to the first dosing.
21. Plasma donation within 7 days prior to the first dosing.
22. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study

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 zero to the time of the last quantifiable concentration (AUC_{last}).
- Area under the concentration-time curve from time zero to infinity (AUC_{∞}).

Secondary Endpoint:

- Incidence of TEAEs.

Exploratory Endpoints:

[redacted]

[redacted]

Statistical Considerations:

Pharmacokinetics:

For each part, natural log (ln)-transformed C_{max}, AUC_{last}, and AUC_{∞} data will be analyzed using a linear mixed effects model, separately. The model with treatment, period, and sequence as fixed effects, and participant nested within sequence as a random effect. The point estimates and the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of C_{max}, AUC_{last}, and AUC_{∞} for the test formulation versus the reference formulation will be calculated using the exponentiation of the point estimates of the differences between treatments and the corresponding 90% CIs from the analyses on the ln-transformed C_{max}, AUC_{last}, and AUC_{∞}.

[redacted].

The comparisons of interest are as follows: Treatment C relative Treatment A; Treatment B relative Treatment A; Treatment E relative Treatment D; Treatment F relative Treatment D.

In Part A, for T3 mini-tablets (Treatment B) and commercial tablets (Treatment C), BE to reference formulation T4 tablets (Treatment A) will be for the AUC_{∞}, AUC_{last}, and C_{max} and is claimed if the 90% CI for the GMRs for these parameters are each within 80.00% and 125.00% for soticlestat. The BE will be tested first between commercial tablets (Treatment C) and reference formulation T4 tablets (Treatment A), then followed with T3 mini-tablets (Treatment B) and reference formulation T4 tablets (Treatment A). In other words, if the 90% CI for AUC_{∞}, AUC_{last}, and C_{max} GMR for soticlestat between commercial tablets (Treatment C) and reference formulation T4 tablets (Treatment A) does not fall within 80.00% and 125.00%, BE cannot be claimed for T3 mini-tablets (Treatment B) and reference formulation T4 tablets (Treatment A) even if the 90% CI for GMR between B and A falls within 80.00% and 125.00%.

Safety:

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics for TEAE, laboratory evaluations, vital signs, and safety 12-lead ECG. Results for C-SSRS will be listed.

Sample Size Justification:

[redacted]

2.0 STUDY SCHEMATIC

Table 2.a Study Design for Part A

S	Period 1			Period 2		Period 3			FU
	C-I and Predose Assessment	Soticlestat Dosing, PK Sampling, and Study Assessments	PK Sampling and Study Assessments	Soticlestat Dosing, PK Sampling, and Study Assessments	PK Sampling and Study Assessments	Soticlestat Dosing, PK Sampling and Study Assessments	PK Sampling and Study Assessments	Study Exit [a] (PK Sampling and Study Assessments)	
Within 28 days prior to first dosing	Day -1	Day 1	Day 2 – 5 [b]	Day 1 [b]	Day 2 – 5 [b]	Day 1 [b]	Day 2 – 4	Day 5	14 (±3) days following last soticlestat dose
	---------- Confinement [c] ----------								

[a] Study Exit is defined as the end of last treatment period.

[b] Day 5 of Period 1 and Period 2 will also be considered Day 1 of Period 2 and Period 3, respectively. Procedures scheduled on both days will only be performed once.

[c] Participants will start the confinement on Day -1 of Period 1 and will remain confined until Day 5 of Period 3. Participants may be admitted earlier than Day 1 for COVID-19 testing not related to study protocol, as per CRU requirements.

Abbreviations: C-I = Check-in, FU = Follow-up, PK = Pharmacokinetics, S = Screening.

Table 2.b Study Treatments for Part A

Treatments	Study Drug	Dose	Dose Regimen	Number of Days on Study Drug
Treatment A (Reference)	Soticlestat T4 tablets	300 mg (3 x 100 mg strength)	Single dose, oral, fast	Day 1 of each period
Treatment B (Test)	Soticlestat T3 mini-tablets	300 mg (15 x 20 mg strength)	Single dose, oral, fast	Day 1 of each period
Treatment C (Test)	Soticlestat commercial tablets	300 mg (1 x 300 mg strength)	Single dose, oral, fast	Day 1 of each period

Table 2.c Study Design for Part B

S	Period 1			Period 2		Period 3			FU
	C-I and Predose Assessment	Soticlestat Dosing, PK Sampling and Study Assessments	PK Sampling and Study Assessments	Soticlestat Dosing, PK Sampling and Study Assessments	PK Sampling and Study Assessments	Soticlestat Dosing, PK Sampling and Study Assessments	PK Sampling and Study Assessments	Study Exit [a] (PK Sampling and Study Assessments)	
Within 28 days prior to first dosing	Day -1	Day 1	Day 2 – 5 [b]	Day 1 [b]	Day 2 – 5 [b]	Day 1 [b]	Day 2 – 4	Day 5	14 (±3) days following last soticlestat dose
	---------- Confinement [c] ----------								

[a] Study Exit is defined as the end of last treatment period.

[b] Day 5 of Period 1 and Period 2 will also be considered Day 1 of Period 2 and Period 3, respectively. Procedures scheduled on both days will only be performed once.

[c] Participants will start the confinement on Day -1 of Period 1 and will remain confined until Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

Abbreviations: C-I = Check-in, FU = Follow-up, PK = Pharmacokinetics, S = Screening

Table 2.d Study Treatments for Part B

Treatments	Study Drug	Dose	Dose Regimen	Number of Days on Study Drug
Treatment D (Reference)	Soticlestat T4 tablets	300 mg (3 x 100 mg strength)	Single dose, oral, fast	Day 1 of each period
Treatment E (Test)	Soticlestat T4 tablets	300 mg (3 x 100 mg strength)	Single dose, oral, fed	Day 1 of each period
Treatment F (Test)	Soticlestat T4 tablets	300 mg (3 x 100 mg strength)	Single dose, oral, crushed and mixed with applesauce, fast	Day 1 of each period

3.0 SCHEDULE OF STUDY PROCEDURES

Table 3.a Part A

Study Procedures [a]	S [b]	Period 1 Only	Study Days in Each Period [c]																		ET [e]	FU [f]
Days →		-1	1													2		3	4	5[d]		
Hours →		C-1 [g]	0	0.167	0.25	0.5	0.75	1	1.5	2	4	6	8	10	12	24	36	48	72	96		
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History/Demography	X																					
Safety Evaluations																						
Physical Examination	X	X																		X [h]	X	
Height	X																					
Weight	X	X																		X [h]	X	
12-Lead Safety ECG	X		X [i]			X			X							X				X [h]	X	
Vital Signs (PR, BP, RR, and T)	X		X [i]			X			X							X				X [h]	X	
Hem, Serum Chem[j], Coag, and UA	X	X																		X [h]	X	
C-SSRS [k]	X	X																		X [h]	X	
Serum Pregnancy Test (females only)	X	X																				
Serum FSH (PMP females only)	X																					
Urine Drug and Alcohol Screen	X	X																				
HIV/Hepatitis Screen	X																					
AE Monitoring	X	X																				X
Concomitant Medication Monitoring	X	X																				X
Soticlestat Dosing / PK																						
Soticlestat Dosing			X [i]																			
Blood for Soticlestat [redacted] PK			X [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [n]		
Other Procedures																						
Confinement in the CRU		X																				
Visit	X																					

a For details on Procedures, refer to Section 9.0.

b Within 28 days prior to the first dosing.

c There will be a washout period of exactly 4 days between each soticlestat dose.

d Day 5 of Periods 1 and 2 will be the same as Day 1 of Periods 2 and 3, respectively. Procedures scheduled on both days will only be performed once.

e To be performed at time of early termination from the study.

f After discharge, the CRU will contact all participants (including participants who terminate the study early) 14 (±3) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any AEs have occurred and/or any concomitant medications were taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

g Participants will be admitted to the CRU on Day -1 of Period 1 and be confined up to Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

h To be performed at the end of Period 3 only.

i To be performed within 24 hours prior to dosing in Period 1 and 2 hours prior to dosing in Periods 2 and 3.

j Samples for serum chemistry will be obtained after 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.

k At screening, the C-SSRS Baseline/Screening version will be administered; at all other time points, the Since Last Visit version will be administered.

l In each period, soticlestat will be administered as per Treatments A, B, or C, as per the randomization sequence. Soticlestat will be administered following an overnight fast of at least 10 hours. Fasting will continue for at least 4 hours postdose.

m To be performed prior to dosing.

n The 96-hour PK sample of Periods 1 and 2 will serve as the predose PK sample of Periods 2 and 3, respectively.

Abbreviations: AE = Adverse event(s), BP = Blood pressure, C-I = Check-in, C-SSRS = Columbia-suicide severity rating scale, Chem = Chemistry, Coag = Coagulation, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, ET = Early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, PK = Pharmacokinetics, PMP = Postmenopausal, PR = Pulse rate, RR = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis.

Table 3.b Part B

Study Procedures [a]	S [b]	Period 1 Only	Study Days in Each Period [c]																				ET [e]	FU [f]
Days →		-1	1															2		3	4	5 [d]		
Hours →		C-1 [g]	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	10	12	24	36	48	72	96		
Administrative Procedures																								
Informed Consent	X																							
Inclusion/Exclusion Criteria	X	X																						
Medical History/Demography	X																							
Safety Evaluations																								
Physical Examination	X	X																				X [h]	X	
Height	X																							
Weight	X	X																				X [h]	X	
12-Lead Safety ECG	X		X [i]			X			X									X				X [h]	X	
Vital Signs (PR, BP, RR, and T)	X		X [i]			X			X									X				X [h]	X	
Hem, Serum Chem [j], Coag, and UA	X	X																				X [h]	X	
C-SSRS [k]	X	X																				X [h]		
Serum Pregnancy Test (females only)	X	X																						
Serum FSH (PMP only)	X																							
Urine Drug and Alcohol Screen	X	X																						
HIV/Hepatitis Screen	X																							
AE Monitoring	X											X												X
Concomitant Medication Monitoring	X											X												X
Soticlestat Dosing / PK																								
Soticlestat Dosing			X [l]																					
Blood for Soticlestat [redacted] PK			X [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [n]		
Other Procedures																								
Confinement in the CRU												X												
Visit	X																							

a For details on Procedures, refer to Section 9.0.

b Within 28 days prior to the first dosing.

c There will be a washout period of exactly 4 days between each soticlestat dose.

d Day 5 of Periods 1 and 2 will be the same as Day 1 of Periods 2 and 3, respectively. Procedures scheduled on both days will only be performed once.

e To be performed at time of early termination from the study.

f After discharge, the CRU will contact all participants (including participants who terminate the study early) 14 (±3) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any AEs have occurred and/or any concomitant medications were taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

g Participants will be admitted to the CRU on Day -1 of Period 1 and be confined up to Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

h To be performed at the end of Period 3 only.

i To be performed within 24 hours prior to dosing in Period 1 and 2 hours prior to dosing in Periods 2 and 3.

j Samples for serum chemistry will be obtained after 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.

k At screening, the C-SSRS Baseline/Screening version will be administered; at all other time points, the Since Last Visit version will be administered.

l In each period, soticlestat will be administered as per Treatments D, E, and or F, as per the randomization sequence. In Treatment D and F, soticlestat will be administered following an overnight fast of at least 10 hours. In Treatment E, soticlestat will be administered following an overnight fast of at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat breakfast. Fasting will continue for at least 4 hours postdose in Treatments D, E, and F.

m To be performed prior to dosing.

n The 96-hour PK sample of Periods 1 and 2 will serve as the predose PK sample in Periods 2 and 3, respectively.

Abbreviations: AE = Adverse event(s), BP = Blood pressure, C-I = Check-in, C-SSRS = Columbia-suicide severity rating scale, Chem = Chemistry, Coag = Coagulation, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, ET = Early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, PK = Pharmacokinetics, PMP = Postmenopausal, PR = Pulse rate, RR = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis.

4.0 INTRODUCTION

4.1 Background

Soticlestat is a potent and selective cholesterol 24S 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 is a cluster of pediatric epilepsy syndromes and includes Dravet Syndrome (DS) and Lennox Gastaut Syndrome (LGS).

Nonclinical Background

Soticlestat was evaluated in a series of nonclinical pharmacology, toxicology, and drug metabolism and PK studies in accordance with relevant Food and Drug Administration (FDA) guidance documents. The results supported investigational new drug (IND) opening study. The complete results from nonclinical studies demonstrated a favorable benefit over the risk potential of soticlestat for further clinical evaluation through Phase 3 studies and registration. Nonclinical study results can be found in the Investigator's Brochure (IB) [1].

Clinical Background

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 subjects with moderate to severe hepatic impairment and healthy subjects, and 3 Phase 3 studies in DS and LGS patients are ongoing.

Overall, 382 subjects 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).

In the 6 completed Phase 1 clinical studies, a total of 116 healthy participants received at least 1 dose of soticlestat. In these studies, soticlestat when administered as a single-dose up to 1350 mg was safe and well tolerated. In the 14-day multiple rising dose study, soticlestat was safe and well tolerated in most healthy participants up to 600 mg daily (either as 600 mg once daily [QD] or 300 mg twice daily [BID], without up-titration). Two participants discontinued study drug due to a TEAE: one with acute psychosis (Cohort 4: soticlestat 600 mg QD) that was reported as severe intensity, and one with mild confusional state (Cohort 3: soticlestat 300 mg BID) occurring on study Day 10. There was no additional treatment required beyond cessation of study drug for these events. No safety issues of concern were identified based on assessments of physical examinations, vital sign measurements, clinical laboratory values, or 12-lead ECG findings. No significant safety issues have been identified in the completed patient studies

TAK-935-2001, TAK-935-2008, TAK-935-2002 (ELEKTRA) and TAK-935-18-002 (ARCADE) or from the ongoing TAK-935-18-001 (ENDYMION 1) study, where all subjects were up-titrated to the target dose of 300 mg BID (or equivalent exposure in pediatric subjects with <60 kg body weight). No deaths have occurred in these studies during treatment.

Soticlestat was rapidly absorbed [redacted] following single-dose (15 to 1350 mg; Study TAK-935-101) [redacted] multiple-dose (100 to 600 mg) under fasting conditions in healthy participants (Study TAK-935-1002). When administered under fed conditions, soticlestat [redacted], 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). [redacted]

The PK profile following single- and multiple-dose administration were further characterized in healthy Japanese participants (Study TAK-935-1004). Soticlestat was rapidly absorbed after administration, [redacted]. 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]

In the human absorption, distribution, metabolism and elimination study (Study TAK-935-1008), urinary excretion was the major route for elimination, with approximately 95% of the dose excreted in urine within 48 hours; however, urinary excretion of the parent drug was 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.

Refer to the IB for more detailed background information on soticlestat [1].

4.2 Rationale for the Proposed Study

Background of Clinical Trial Formulation

Soticlestat is formulated for oral administration BID. The formulations used in Phase 2 and Phase 3 clinical studies were tablets and/or mini-tablets. The actual tablet formulations administered in each clinical study and their quantitative components are provided in Table 4.a.

Table 4.a Soticlestat Tablet Formulations Utilized in Phase 2 and Phase 3 Clinical Studies

Components		Quantity per Tablet (mg)		
	Tablet Strength	**100 mg**	**100 mg**	**20 mg**
	Formulation Name	**T2**	**T4**	**T3**
	Clinical Studies	**Phase 2**	**Phase 3**	**Phase 2/ Phase 3**
Tablet Core	TAK-935	100	100	20
Tablet Core	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appearance		Yellow-red film-coated tablets	Light yellow-red film-coated tablets	Yellow-red film-coated tablets

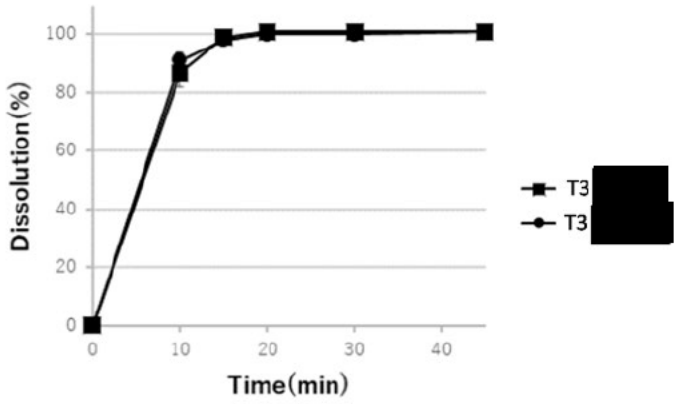
q.s.: quantum sufficit

The soticlestat drug product formulations utilized for Phase 3 clinical studies are light yellow-red film-coated, immediate-release tablets of 100 mg strength (T4 formulation) and yellow-red film-coated round mini-tablets of 20 mg strength (T3 formulation) as seen in Table 4.a. [redacted]. T3 formulations was developed to facilitate ease of swallowing and flexible, weight-based dosing in children and used in Phase 2 studies. The drug product lots for clinical use are packaged in high-density polyethylene bottles equipped with child-resistant caps and induction sealed.

Dissolution profiles of T2, T3, and T4 tablets showed immediate release of soticlestat within 30 minutes (Figure 4.a and Figure 4.b). There is no significant difference in T2 and T4

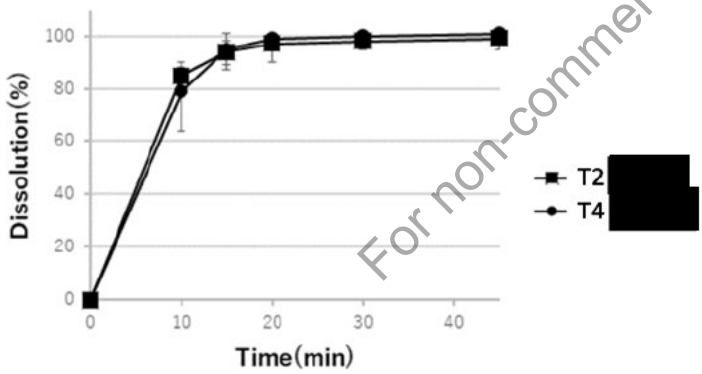
dissolution profiles. Also, these data indicated manufacturing site has no impact on the dissolution profiles of the tablets [redacted].

Figure 4.a Dissolution Profile of 20 mg Tablets (T3)



Dissolution test conditions
Medium: JP 2nd fluid, 37°C 900 mL
Apparatus: USP Apparatus 2, paddle, 50 rpm

Figure 4.b Dissolution Profile of 100 mg Tablets (T2, T4)



Dissolution test conditions
Medium: JP 2nd fluid, 37°C 900 mL
Apparatus: USP Apparatus 2, paddle, 50 rpm

Background for Commercial Formulation

The anticipated therapeutic dosing regimens of soticlestat include 100, 200 and 300 mg BID in commercial setting. To support market formulation supply, new tablets of 200 and 300 mg were developed. Soticlestat 200 and 300 mg tablets are [redacted]. Soticlestat 200 and 300 mg tablets have completely dose-proportional compositions with 100 mg T4 tablets used in Phase 3 studies for 'core' tablet components. Dissolution profiles in various media for 300 mg tablets and 100 mg tablets showed ≥ 97% dissolution within 30 minutes (investigational data on file), [redacted].

Table 4.b [redacted]

4.2.1 Rationale for Part A

The anticipated soticlestat dosing regimen is an up-titration regimen based on participant's tolerability. Three titration doses in the ongoing Phase 3 studies in adults are 100, 200, and 300 mg BID. In children, there are also three titration doses in each body weight category matching the three reference doses in adults. Thus, each soticlestat dosing is administered by 100 mg tablets (T4) or multiple 20 mg mini-tablets (T3) as calculated by each child's body weight.

To minimize the number of tablets in adults and/or children, 200 and 300 mg tablets have been developed for commercial use. The present study is to demonstrate the BE of tablets used in Phase 3 studies (ie, 100 mg tablets and 20 mg mini-tablets) and to-be-marketed tablets of highest strength (ie, 300 mg tablets). [redacted]

4.2.2 Rationale for Part B

Previously, a food effect study (TAK-935-1005) was conducted for 300 mg soticlestat administered as 3 x 100 mg T1 tablets, with an earlier formulation T1, [redacted].

As 100 mg T1 tablet formulation is different from the 100 mg T4 tablet formulation, the Part B of the present study is to evaluate the effect of food on the BA of 300 mg soticlestat given as 3 x 100 mg T4 tablets. [redacted]

Additionally, in the ongoing soticlestat Phase 3 studies, the T4 tablets may be crushed and mixed well in applesauce, yogurt, or other liquid of similar consistency before dosing. Thus, the Part B of the present study is also to assess the effect of tablets crushed and mixed with applesauce on soticlestat PK.

4.3 Benefit/Risk Profile

The dose of 300 mg soticlestat is the recommended Phase 3 dose and will be administered as a single-dose in this study. In addition, doses up to 1350 mg were administered in healthy participants and was found to be safe and well tolerated [1].

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 examination) 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 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 Objectives

Part A:

- To assess the BE of 300 mg soticlestat administered as T3 mini-tablets (Treatment B) compared to 300 mg soticlestat administered as T4 tablets (Treatment A).
- To assess the BE of 300 mg soticlestat administered as commercial tablets (Treatment C) compared to 300 mg soticlestat administered as T4 tablets (Treatment A).

Part B:

- To assess the effect of food on the BA of 300 mg soticlestat administered as T4 tablets under fed condition (Treatment E) compared to fasting condition (Treatment D).

- To assess the effect of tablet crushing on the PK of 300 mg soticlestat administered as T4 tablets crushed and mixed with applesauce (Treatment F) compared to whole T4 tablets (Treatment D).

5.2.2 Study Secondary Objective

- To evaluate the safety and tolerability of soticlestat following single oral dose of 300 mg soticlestat in Treatments A, B, C, D, E, and F.

5.2.3 Study Exploratory Objectives

[redacted]

5.3 Endpoints

5.3.1 Primary Endpoints

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

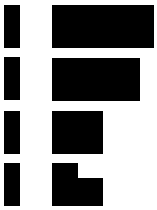
- Maximum observed concentration (C_{max}).
- Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{last}).
- Area under the concentration-time curve from time zero to infinity (AUC_{∞}).

5.3.2 Secondary Endpoint

- Incidence of TEAEs.

5.3.3 Exploratory Endpoints

[redacted]



6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a 2-part, open-label study conducted in healthy adult participants. Part A will evaluate the BE of 3 different soticlestat oral tablet formulations. Part B will evaluate the effect of food and tablet crushing on soticlestat PK.

Each part will be conducted independently as a randomized, 3-period, crossover design. Study schematics of the study design are shown in Table 2.a, Table 2.b, Table 2.c, and Table 2.d. A schedule of assessments is shown in Schedule of Study Procedures (Section 3.0).

The two study parts may be conducted concurrently. Participants can only participate in one study part.

Part A:

Participants will be screened within 4 weeks (28 days) prior to the first dosing (Day -28 to first dosing on Day 1 of Period 1). Upon completion of screening, qualified participants will be admitted to the study site Day -1 of Period 1 and will remain confined until completion of study procedures on Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

In each period, on Day 1, participants will receive a single oral dose of 300 mg soticlestat administered as T4 tablets (Treatment A), T3 mini-tablets (Treatment B), or commercial tablets (Treatment C), in a 3-way crossover fashion. Blood samples for the PK of soticlestat [redacted] will be collected at schedules time points from predose through 96 hours postdose. There will be a washout period of exactly 4 days between each soticlestat doses.

Safety and tolerability will be assessed throughout the study by TEAEs, clinical laboratory evaluations, physical examinations, C-SSRS, 12-lead ECG, and vital signs.

After discharge, the CRU will contact all participants (including participants who terminate the study early) 14 (±3) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any AEs have occurred and/or any concomitant medications were taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

Part B:

Participants will be screened within 4 weeks (28 days) prior to the first dosing (Day -28 to first dosing on Day 1 of Period 1). Upon completion of screening, qualified participants will be admitted to the study site Day -1 of Period 1 and will remain confined until completion of study

procedures on Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

In each period, on Day 1, participants will receive a single oral dose of 300 mg soticlestat administered as intact T4 tablets under fasting conditions (Treatment D), intact T4 tablets under fed condition (Treatment E), or as crushed T4 tablets mixed with applesauce under fasting conditions (Treatment F), in a 3-way crossover fashion. Blood samples for the PK of soticlestat [redacted] will be collected at schedules time points from predose through 96 hours postdose. There will be a washout period of exactly 4 days between each soticlestat doses.

Safety and tolerability will be assessed throughout the study by TEAEs, clinical laboratory evaluations, physical examinations, C-SSRS, 12-lead ECG, and vital signs.

After discharge, the CRU will contact all participants (including participants who terminate the study early) 14 (±3) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any AEs have occurred and/or any concomitant medications were taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

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

This is a 2-part study conducted in healthy adult participants. Part A will evaluate the BE of 3 different soticlestat oral tablet formulations. Part B will evaluate the effect of food and tablet crushing on soticlestat PK. Each part will be conducted independently as a randomized, 3-period, William Square crossover design. Participants will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to reduce the residual variability as every participant acts as their own control. There will be a washout period of 4 days between the soticlestat doses and is considered sufficient to prevent carryover effects of the preceding treatment.

6.4.2 Rationale for Dose

The dose of soticlestat selected for this 2-part study is 300 mg, the recommended Phase 3 dose. In clinical studies, soticlestat when administered as a single-dose up to 1350 mg was safe and well tolerated by healthy participants. The increase in soticlestat exposure from 300 mg to 1350 mg is >4-fold. Taken together the dose is not anticipated to cause any risk or benefit to the subjects participating in this study.

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, C-SSRS, 12-lead ECGs, clinical laboratory evaluations, and physical examinations.

6.4.4 Future Biomedical Research

Any residual plasma samples will be stored by the Sponsor or Bioanalytical facility for the maximal 5 years determined by the Sponsor following the last dosing. Tubes or containers will be identified with a barcode using an appropriate label.

No diseases/conditions, deoxyribonucleic acid, or ribonucleic acid will be analyzed in this study. The analyses will focus on PK profiling for soticlestat [redacted]. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses, and PK and statistical analysis of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

By signing the ICF, participants agree to the possible future analysis of these samples. At any time, the participants can contact the CRU staff to request destruction of the residual samples once PK assessments required to meet the study objective are completed. Any additional research on these samples unspecified by this protocol will require approval from the participants.

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 as close to the scheduled times defined in this protocol as possible.

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

The dose and administration of the study drugs to any participant may not be modified. Unscheduled procedures might be performed for safety reasons. 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 contact 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

Celerion reserves 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 for any reason.

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

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

1. Healthy, adult, male or female of non-childbearing potential (Appendix D), 18 to 55 years of age, inclusive, at screening.
2. Male agrees to comply with any applicable contraceptive requirements of the protocol as detailed in Appendix D.
3. BMI ≥ 18.0 and ≤ 32.0 kg/m^2 at screening.
4. Continuous non-smoker who has not used nicotine-containing products for at least 90 days prior to the first dosing.
5. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs and ECGs, as deemed by the Investigator or designee.
   - Supine blood pressure is ≥ 90/40 mmHg and ≤ 140/90 mmHg at screening;
   - Supine heart rate is ≥ 45 bpm and ≤ 100 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;
   - Estimated creatinine clearance ≥ 80 mL/min at screening.
   - LFT including ALT or AST ≤ 1.5 X the ULN at screening and check-in.
6. Able to swallow multiple tablets.
7. Understands the study procedures in the ICF, and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

Participants must not be enrolled in the study if they meet any of the following criteria prior to the first dosing:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History or presence of gastritis, GI tract, gastric bypass surgery, or hepatic disorder or other clinical condition which, in the opinion of the Investigator or designee, may affect the absorption, distribution, metabolism, or elimination of study drug.

4. History or presence of any of the following, deemed clinically significant by the Investigator or designee:
    - GI disorder (eg peptic ulcer disease, gastroesophageal reflux disease, impaction, chronic constipation, inflammatory bowel disease, ischemic colitis, vascular intestinal atherosclerosis, previous bowel resection, bowel obstruction, bariatric surgery, cholecystitis, intestinal ulceration or inflammation);
    - GI bleeding or perforation;
    - Recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding).
5. History or presence of cataracts.
6. History or presence of other clinically significant vision disturbances as judged by the Investigator or designee.
7. History or presence of epilepsy, seizure, or convulsion, tremor or related symptoms that are deemed clinically significant by the Investigator or designee.
8. 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.
9. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
10. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds.
11. Any positive responses on the C-SSRS that in the clinical judgement of the Investigator has a risk of suicide or has made a suicide attempt in the previous 12 months prior to the first dosing.
12. Female participant of childbearing potential.
13. Female participant with a positive pregnancy test at screening or check-in or who is lactating.
14. Positive urine drug or alcohol results at screening or check-in.
15. Positive results at screening for HIV, HBsAg or HCV.
16. Unable to refrain from or anticipates the use of:
    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing. Thyroid hormone replacement medication may be permitted if the participant has been on the same stable dose for the immediate 3 months prior to the first dosing.
    - Any drugs known to be significant inducers of CYP3A, CYP2C19, UGT1A9 or UGT2B4 enzymes and/or P-gp, including St. John's Wort, within 28 days prior to the first dosing.

Appropriate sources (eg, Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamics interaction with study drug.

17. History of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to the following: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz] per day).
18. Consumes excessive amounts, defined as greater than 4 servings (1 serving is approximately equivalent to 120 mg of caffeine), of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
19. 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 the first dosing and throughout the study.
20. Donation of blood or significant blood loss within 56 days prior to the first dosing.
21. Plasma donation within 7 days prior to the first dosing.
22. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2 and throughout the study, including the follow-up period. After the first dose, ibuprofen (up to 1.2 g per 24 hour period) may be administered at the discretion of the Investigator or designee. Thyroid hormone replacement medication may be permitted if the participant has been on the same stable dose for the immediate 3 months prior to the first dosing.

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.

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

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 First Dosing (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from first dosing until the end of PK collection
Xanthine and/or caffeine	Prohibited from 72 hours prior to first dosing [a]	Prohibited from first dosing until the end of PK collection [a]
Medications	See Sections 7.1 and 7.2	See Sections 7.1 and 7.2
Nicotine- and tobacco-containing and/or cannabis products	Prohibited from 90 days prior to first dosing	Prohibited from first dosing until the follow-up visit
Food substance		
Grapefruit/Seville orange	Prohibited from 14 days prior to first dosing	Prohibited from first dosing until the end of PK collection.
Other Fruit Juice	Prohibited from 12 hours prior to first dosing	Prohibited from first dosing until end of PK collection.
Vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	Prohibited from 7 days prior to first dosing	Prohibited from first dosing until end of PK collection.

[a] small amounts of caffeine derived from normal foodstuffs eg, 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 each dosing) will be restricted 1 hour prior to and 1 hour after each 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.

Part A:

On Day 1 of each period, participants will fast overnight for at least 10 hours prior to dosing and 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.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time in each period.

Part B:

On Day 1 of Treatment D, participants will fast overnight for at least 10 hours prior to Day 1 dosing and will continue the fast for at least 4 hours postdose.

On Day 1 of Treatment E, participants will be required to fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat breakfast which will be entirely consumed within 30 minutes. An example of high-fat breakfast would be 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 240 mL of whole milk [2]. Participants will fast for at least 4 hours postdose.

On Day 1 of Treatment F, participants will fast overnight for at least 10 hours prior to dosing, where a single-dose of soticlestat will be administered orally after being crushed and mixed with 6 teaspoons or 30 mL of applesauce. Participants will fast for at least 4 hours postdose.

The instructions for crushing soticlestat tablets:

- Three 100 mg tablets will be crushed and mixed with 6 teaspoons or 30 mL of applesauce.
- After crushing, it should be dosed within 2 hours after mixing. Storage is allowed under room light conditions, without strict shading.
- The crushing operation should be done as described in the instruction manual.

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.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition (except for the meal served as part of Treatment E and the applesauce Treatment F) and will be taken at approximately the same time in each period.

7.4.2 Activity

Participants will remain seated for the first 4 hours postdose, 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 post soticlestat dose, participants may be allowed to rise for brief periods under supervision (eg, 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.

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.

   LFT Abnormalities:

   Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a participant's laboratory profile has returned to normal/baseline status, see Section 9.2.7, if the following circumstances occur at any time during study drug treatment:

   - ALT or AST >8 x ULN, or
   - ALT or AST >5 x ULN and persists for more than 2 weeks, or
   - ALT or AST >3 x ULN in conjunction with elevated total bilirubin >2 x ULN or international normalization ratio (INR) >1.5, or
   - ALT or AST >3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

   QTcF interval:

   Study drug should be discontinued immediately with appropriate clinical follow-up if a QTcF interval >500 msec or if there is an increase of QTcF >60 msec above baseline detected by ECG and confirmed with a repeat ECG. 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: Attempt to contact the participants were unsuccessful. Attempts to contact the participants must be documented in the participant's source documents.
4. Voluntary withdrawal: The participants (or participant's legally acceptable representative) wishes 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 coronavirus disease 2019 (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.
8. 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 CRFs.

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 to ensure a minimum of 66 and 18PK-evaluable participants complete Part A and Part B of the study, respectively.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Investigational Medicinal Products:

Product Name:	Soticlestat (TAK-935)
Strength:	20 mg, 100 mg, and 300 mg
Dose:	300 mg
Dosage Form/Formulations:	20 mg T3 mini-tablet
	100 mg T4 tablet
	300 mg commercial 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 Sponsor will supply sufficient quantities of soticlestat to allow completion of this study. For Part A, sufficient quantities of soticlestat will also be included for the retention of testing samples as per FDA 21 CFR 320 and Guidance for Industry: Handling and Retention of BA and BE testing Samples [3].

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drugs 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 Sequence

Part A and Part B are each based on a 3 x 6 x 3 Williams square crossover design.

The following randomization sequence (Table 8.a and Table 8.b) will be available to the CRU pharmacy staff that is preparing the study drugs.

Table 8.a Randomization Sequence in Part A

Sequence	N	Period 1	Period 2	Period 3
1	12	B	A	C
2	12	A	C	B
3	12	C	B	A
4	12	B	C	A
5	12	A	B	C
6	12	C	A	B

N: number of participants
Treatment A: 3 x 100 mg T4 tablets, fasted (Reference)
Treatment B: 15 x 20 mg T3 mini-tablets, fasted (Test)
Treatment C: 1 x 300 mg commercial tablet, fasted (Test)

Table 8.b Randomization Sequence in Part B

Sequence	N	Period 1	Period 2	Period 3
1	4	E	D	F
2	4	D	F	E
3	4	F	E	D
4	4	E	F	D
5	4	D	E	F
6	4	F	D	E

N: number of participants
Treatment D: 3 x100 mg T4 tablets, fasted (Reference)
Treatment E: 3 x100 mg T4 tablets, fed (Test)
Treatment F: 3 x100 mg T4 tablets crushed and mixed with applesauce, fasted (Test)

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, 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 Randomization 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 randomization identification number at the time of the first dosing, different from the screening number and will receive the corresponding product, according to a randomization sequence.

If replacement participants are used, the replacement participant number will be 100 more than the original (eg, Participant No. 101 will replace Participant No. 1).

9.1.1.2 Study Drug Assignment

All participants will receive the treatments as detailed in Section 9.2.6.

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, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.2 and 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 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 Physical Exam

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or Sponsor for reasons related to participant safety.

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, blood pressure and pulse rate, 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 (5 minutes).

Vital signs will be measured within 24 hours prior to Day 1 dosing of Period 1 for the predose time point. At all other predose time points, vital signs will be measured within 2 hours prior to dosing. 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. All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing of Period 1 for the predose time point. At all other predose time points, ECGs will be measured within 2 hours prior to dosing. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Study Drug Administration

Soticlestat formulation will be provided as described in Section 8.1.

Dose regimens for study drugs are described in Table 2.a, Table 2.b, Table 2.c, and Table 2.d.

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. Mini-tablets will be taken in multiple at one time. If the study drugs cannot all be swallowed at the same time, up to a maximum of 50 mL of additional water may be administered as required by the subject, however, dosing should be completed within approximately 3 minutes.

Additional information regarding drug preparation and administration may be provided in a separate document.

Participants will be instructed not to crush, split, or chew the tablets except for Treatment F. Tablets in Treatment F will be administered crushed and mixed in applesauce.

The exact clock time of dosing will be recorded.

A qualified designee will be responsible for monitoring the administration of the assigned doses. A mouth check will be performed by the qualified designee to ensure that the participants have swallowed the study drug(s). Once a participant has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the participant's mouth. Participants' hands will also be verified to ensure that the study drug(s) was ingested.

9.2.7 C-SSRS

Suicidal ideation will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures for each study part (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. It is recommended that the same rater be used to administer the scale to the participant at all time points when C-SSRS is scheduled. 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.

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
Erythrocytes	Mean platelet volume
Total and differential leukocyte count	Immune cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)

Coagulation

Coagulation test will be conducted as outlined in the Schedule of Study Procedures (Section 3.0). Coagulation test will consist of the following tests:

Activated partial thromboplastin time (aPPT)
Prothrombin time / INR

Chemistry

Serum chemistry tests will be performed 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 being taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Blood Urea Nitrogen	Albumin
Bilirubin (total, direct, and indirect)	Sodium
Alkaline phosphatase	Potassium
AST	Chloride
ALT	Glucose
Calcium	Creatinine *
Carbon dioxide	Phosphate
Protein (total)	Alpha1-acidic glycoprotein (screening only)
Gamma-glutamyl transferase	Magnesium
Urea	

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

Urinalysis

Urinalysis will consist of the following tests:

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

* 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 drug screen
HBsAg	Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone)
HCV *(if antibody positive, confirm RNA negative)*	Amphetamines
Urine alcohol screen	Barbiturates
Serum pregnancy test (for females only)	Benzodiazepines
FSH (for postmenopausal females only)	Cocaine
COVID-19 (SARS-CoV-2 polymerase chain reaction test or equivalent)	Cannabinoids
	Buprenorphine/metabolite
	Methadone/metabolite
	Oxycodone/oxymorphone
	Phencyclidine

9.3 Pharmacokinetic Samples

Samples for assessment of soticlestat [redacted], will be collected as delineated in Section 3.0.

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 soticlestat [redacted] PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory

9.3.1 Pharmacokinetic 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 NCA. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

Remaining plasma volume from the PK samples may be pooled across subjects and time points to create pools of plasma to use for assay cross-validation activities consistent with the scope of the 2018 bioanalytical method validation guidance [4].

9.3.1.1 Plasma for PK Measurements

The following PK parameters will be calculated from plasma concentrations of soticlestat [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]

[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 housed on Day -1 of Period 1, at the time indicated by the CRU, until after the last blood draw and/or study procedures on Day 5 of Period 3. Participants may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol, as per CRU requirements.

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

The CRU will contact all participants (including participants who terminate the study early) 14 (±3) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any AEs have occurred and/or any concomitant medications have been taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

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.

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 first administration of study medication and 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 pneumonia	
COVID-19-related disease	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.

In addition, relationship (causality) to COVID-19 should be determined for all PTEs and AEs. The relationship should be assessed as related if the Investigator considers that there is reasonable possibility that an event is due to COVID-19. Otherwise, the relationship should be assessed as not related.

Similarly, relationship (causality) to COVID-19 vaccines should be determined for all PTEs and AEs. The relationship should be assessed as related if the Investigator considers that there is reasonable possibility that an event is due to COVID-19 vaccines. Otherwise, the relationship should be assessed as not related. If the AE has relationship to vaccination, specific verbatim term should be used, eg, post-vaccination fever, vaccination site burning.

In addition, if the causality assessment done by the Investigator determines that the event or events (PTEs or AEs) are related or possible related to COVID-19 or the COVID-19 vaccine, the events should be assessed as not related to the investigational product. If the AE is related to COVID-19 vaccination, specific verbatim term(s) should be used, eg, post-vaccination fever, vaccination site burning.

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.

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.
- 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, Special Interest AEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, 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 14 (± 3) days after the last dose of soticlestat. 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 first 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 first 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]).
- Relationship to COVID-19.
- Relationship to COVID-19 vaccine.
- 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 Section 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 first 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

There are no AEs of Special Interest for soticlestat.

10.2.8.5 Reporting of Abnormal LFTs

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 9.2.9 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 statistical analysis plan (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 PK analysis set. More details will be provided in SAP.

11.1.1.2 Safety Set

All participants who received at least one dose of the study drug(s) will be included in the safety analysis set. More details will be provided in SAP.

11.1.2 Analysis of Demography and Other Baseline Characteristics

11.1.3 PK Analysis

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

Values will be reported for the plasma soticlestat [redacted] concentrations for each participant. PK parameters for plasma concentrations of soticlestat [redacted] will be calculated as described in Section 9.3.1.1, and outlined in the SAP.

11.1.3.1 Linear Mixed Effects Model

For each part, ln-transformed C_{max}, AUC_{last}, and AUC_{∞} data will be analyzed using a linear mixed effects model, separately. The model will include treatment, period, and sequence as fixed effects, and participants nested within sequence as a random effect. The point estimates and the

90% CIs for the GMRs of C_{max}, AUC_{last}, and AUC_{∞} for the test formulation versus the reference formulation will be calculated using the exponentiation of the point estimates of the differences between treatments and the corresponding 90% CIs from the analyses on the ln-transformed C_{max}, AUC_{last}, and AUC_{∞}.

[redacted].

The comparisons of interest are as follows:

<u>BE:</u>

- Treatment C compared with Treatment A.
- Treatment B compared with Treatment A.

<u>Food effect:</u>

- Treatment E compared with Treatment D.

<u>Tablet crushing:</u>

- Treatment F compared with Treatment D.

11.1.3.2 Bioequivalence

In Part A, for T3 mini-tablets (Treatment B) and commercial tablets (Treatment C), BE to reference formulation T4 tablets (Treatment A) will be for the AUC_{∞}, AUC_{last}, and C_{max} and is claimed if the 90% CI for the GMRs for these parameters are each within 80.00% and 125.00% for soticlestat. The BE will be tested first between commercial tablets (Treatment C) and reference formulation T4 tablets (Treatment A), then followed with T3 mini-tablets (Treatment B) and reference formulation T4 tablets (Treatment A). In other words, if the 90% CI for AUC_{∞}, AUC_{last}, and C_{max} GMR for soticlestat between commercial tablets (Treatment C) and reference formulation T4 tablets (Treatment A) does not fall within 80.00% and 125.00%, BE cannot be claimed for T3 mini-tablets (Treatment B) and reference formulation T4 tablets (Treatment A) even if the 90% CI for GMR between B and A falls within 80.00% and 125.00%.

11.1.3.3 [redacted]

[redacted]

11.1.4 PD Analysis

Not applicable.

11.1.5 Safety Analysis

All safety data will be populated in the individual CRFs.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

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 treatment 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.

11.1.5.2 Clinical Laboratory Evaluation

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

11.1.5.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

11.1.5.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by treatment and point of time of collection.

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.

C-SSRS results will listed by participant.

11.2 Interim Analysis and Criteria for Early Termination

Not applicable.

11.3 Determination of Sample Size

[redacted]

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Due to COVID-19, monitoring visits may also be conducted remotely. 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 (as long as blinding is not jeopardized), 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.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the 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 Investigator's Brochure, 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 participants 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 informed consent form 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 informed consent form 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 informed consent form 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 informed consent form, 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 informed consent form, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

All revised informed consent forms 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 informed consent form.

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 America's 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. Email: PVSafetyAmericas@tpna.com Fax: 224-554-1052

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 [R2] Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events 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.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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

%	Percentage
[redacted]	[redacted]
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{∞}	The area under the concentration-time curve, from time 0 to infinity
[redacted]	[redacted]
AUC_{last}	The area under the concentration-time curve, from time 0 to the last quantifiable concentration
BA	Bioavailability
BE	Bioequivalence
BID	Twice daily
BMI	Body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CDD	CDKL5 deficiency disorder
CDKL5	Cyclin-dependent kinase-like 5
CFR	Code of Federal Regulations
CH24H	Cholesterol 24S hydroxylase
CI	Confidence interval
[redacted]	[redacted]
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CI	Confidence interval
CRF	Case report form
CRU	Clinical Research Unit
CV	Coefficient of variance
CYP	Cytochrome P450
DEE	Developmental and Epileptic Encephalopathies
DS	Dravet Syndrome
Dup15q	15q11-q13 duplication syndrome
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone

GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ln	Natural log
LGS	Lennox Gastaut Syndrome
LFT	Liver function test
LSM	Least-square mean
MedDRA®	Medical Dictionary for Regulatory Activities®
NCA	Non-compartmental analysis
NDA	New drug application
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PTE	Pretreatment event
QD	Once daily
QTcF	QT interval corrected for pulse rate using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
T3	Yellow-red film-coated round mini-tablets of 20 mg strength
T4	Yellow-red film-coated, immediate-release tablets of 100 mg strength
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
[redacted]	[redacted]

15.0 DATA HANDLING AND RECORD KEEPING

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 Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between Celerion and the Sponsor (eg, electronically, CD, flashdrive, SFTP). This will be documented in the Data Management Plan (if applicable).

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 informed consent forms, participant authorization forms regarding the use of personal health information (if separate from the informed consent forms), 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. Addendum 1, 03 February 2022, for Edition 7, 31 January 2022.
2. Food and Drug Administration: Center for Drug Evaluation and Research (CDER). Guidance for Industry: Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations (Draft Feb 2019). Available at: https://www.fda.gov/media/121313/download
3. Food and Drug Administration. Guidance for Industry: Handling and Retention of Bioavailability BA and Bioequivalence BE Testing Samples (May 2004). Available at: https://www.fda.gov/media/71393/download.
4. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry: Bioanalytical Method Validation (May 2018). Available at: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are participant 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 Code of Federal Regulation (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 participant 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 informed consent form 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 informed consent form 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 informed consent form, 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 informed consent form 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. Regular pregnancy tests will be performed throughout the study for all female participants.

25. Male participants are not required to use barrier contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 90 days after the last dose 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

Male subjects who participate in the study are not required to use barrier contraception. Separately, donation of sperm is not allowed during the study and within 90 days following the last administration of the study drug.

Female Participants and Their Male Partners

Only women of non-childbearing potential will be included in this study. A female of non-childbearing potential, must have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:

- hysteroscopic sterilization;
- bilateral tubal ligation or bilateral salpingectomy;
- hysterectomy;
- bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and FSH serum levels consistent with postmenopausal status*. *Definitions and Procedures for Contraception and Pregnancy Avoidance*

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, 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.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Assessment of 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?

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 the last dose, 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 male 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

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

Summary of Changes Since Last Version of Approved Protocol	
Description of Change	**Sections Affected by Change**
The protocol is amended to add C-SSRS safety evaluations as requested by the Advarra Institutional Review Board (IRB) based on the communication dated 01 March 2022. The protocol is updated to include assessment of C-SSRS at screening, check-in (Day -1), and at the end-of-study or at the time of early termination.	Section 1.0 (Study Summary). Section 3.0 (Schedule of Study Procedures). Section 4.3 (Benefit/Risk Profile). Section 6.1 (Study Design). Section 6.4.3.2 (Safety Endpoints). Section 7.2 (Exclusion Criteria), exclusion criterion #11 is added. Section 9.2.7 (C-SSRS). Section 11.1.5.4 (Other Safety Parameters). Section 14.1.4 (List of Abbreviations).
Details were added for the pooling of plasma samples to harmonize with the 2018 bioanalytical method validation guidance.	Section 9.3.1 (Pharmacokinetic Measurements).
The protocol is updated to only conduct Day -1 procedures in Period 1, and to remove the following Day 4 procedures: physical examination, weight, and safety laboratories (hematology, serum chemistry, coagulation, and urinalysis).	Section 3.0 (Schedule of Study Procedures).
The protocol is updated to clarify that study drug should be discontinued immediately with appropriate clinical follow-up if there is an increase of QTcF >60 msec above baseline.	Section 7.5 (Criteria for Discontinuation or Withdrawal of a Participant)

Summary of Changes Since Last Version of Approved Protocol	
Description of Change	**Sections Affected by Change**
The protocol is updated to correct formatting and typos/grammatical errors.	Section 1.0 (Study Summary). Section 2 (Study Schematic). Section 3.0 (Schedule of Study Procedures). Section 4.3 (Benefit/Risk Profile). Section 6.6.3 (Definition of Study Completion). Section 6.4.4 (Future Biomedical Research).

Amend 01 to A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Bioequivalence of Soticlestat Oral Tablet Formulations and the Effect of Food and Tablet Crushing on the Pharmacokinetics of Soticlestat in Healthy Adult Participants

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	21-Mar-2022 13:59 UTC
[redacted]	Clinical VP Approval	21-Mar-2022 14:10 UTC
[redacted]	Biostatistics Approval	21-Mar-2022 14:25 UTC