Statistical Analysis Plan

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

Document Version and Date: Original Version, 22-March-2022

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.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-935-1014

Celerion Study Number: CA33006

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

Phase 1

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Electronic signature can be found on the last page of this document.

Study 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

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{∞_pred}	area under the concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration
[redacted]	[redacted]
$AUC_{extrap\%\_pred}$	area under the curve from the last quantifiable concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred}
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
CI	confidence interval
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
$CL/F_{\_pred}$	apparent clearance after extravascular administration, calculated using the predicted value of the last quantifiable concentration
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	percent coefficient of variation
DMP	data management plan
ECG	electrocardiogram
Geom CV%	geometric coefficient of variation
Geom Mean	geometric mean
GMR	geometric mean ratio
ICF	informed consent form
LSM	least-squares mean
ln	natural log
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
n	number of observations
PK	pharmacokinetic

PRO	Patient Reported Outcome
PT	Preferred Term (MedDRA)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SOC	System Organ Class
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
[redacted]	[redacted]
[redacted]	[redacted]
$V_z/F_{\_pred}$	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the predicted value of the last quantifiable concentration
WHO	World Health Organization
[redacted]	[redacted]

Note: The PK parameters presented in the clinical study report (CSR) and in the in-text tables will be subscripted, whereas the PK parameters presented in the end-of-text tables will not be subscripted. In addition, AUC_{∞}, AUC_{∞_pred}, [redacted] will be presented as AUCinf, AUCinf_pred, [redacted] in the end-of-text tables, respectively.

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

Part A:

- *To assess the bioequivalence (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 pharmacokinetics (PK) of 300 mg soticlestat administered as T4 tablets crushed and mixed with applesauce (Treatment F) compared to whole T4 tablets (Treatment D).*

1.1.2 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.*

1.1.3 Exploratory Objectives

- [redacted]
- [redacted]

1.2 Endpoints

Note: The calculation of AUC_{∞}, [redacted] are based on the observed value of the last quantifiable concentration unless stated otherwise.

1.2.1 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 0 to the time of the last quantifiable concentration (AUC_{last})*

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

1.2.2 Secondary Endpoint

- *Incidence of treatment-emergent adverse events (TEAEs)*

1.2.3 Exploratory Endpoints

[redacted]

1.2.4 Additional Endpoints

The following PK parameters will be calculated for soticlestat [redacted], as appropriate:

- Area under the concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration (AUC_{∞_pred}).
- Area under the curve from the last quantifiable concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred} ($AUC_{extrap}\%_{\_pred}$).

- Apparent clearance after extravascular administration, calculated using the predicted value of the last quantifiable concentration ($CL/F_{\_pred}$) for soticlestat only.
- Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the predicted value of the last quantifiable concentration ($V_z/F_{\_pred}$) for soticlestat only.

[redacted].

1.3 Estimand(s)

Not applicable.

2.0 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.d, and Table 2.e. The two study parts may be conducted concurrently. Participants can only participate in one study part.

Note: One (1) study site will be used (Celerion, Phoenix, Arizona), but an additional site (Celerion, Lincoln, Nebraska) may be engaged to aid in recruiting, if needed.

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 coronavirus disease 2019 (COVID-19) testing not related to study protocol, as per clinical research unit (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, Columbia-Suicide Severity Rating Scale (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 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.

The study schematic for Part A is presented in the Table 2.a:

Table 2.a Study Design for Part A

S	Period 1			Period 2		Period 3			Follow-up
	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, PK = Pharmacokinetics, S = Screening

The study treatments for Part A are presented in Table 2.b:

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

The randomization sequences for Part A is presented in Table 2.c:

Table 2.c 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)

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.

The study schematic for Part B is presented in Table 2.d:

Table 2.d Study Design for Part B

S	Period 1			Period 2		Period 3			Follow-up
	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, PK = Pharmacokinetics, S = Screening

The study treatments for Part B are presented in Table 2.e:

Table 2.e 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

The randomization sequences for Part B is presented in Table 2.f:

Table 2.f 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)

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

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 geometric mean ratios (GMRs) for all of these parameters are each within 80.00% and 125.00% for soticlestat. Serial gatekeeping will be used to control overall type 1 error (alpha = 0.05) such that *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},* or *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%.*

The hypotheses to be tested to demonstrate BE between test (T) and reference (R) formulations for a given PK parameter are:

Null hypothesis: $\mu_T - \mu_R < \ln(0.8)$ or $\mu_T - \mu_R > \ln(1.25)$

Alternative hypothesis: $\mu_T - \mu_R \geq \ln(0.8)$ and $\mu_T - \mu_R \leq \ln(1.25)$

where μ_T and μ_R are the population means of the natural log (ln)-transformed parameter for the test formulation, T, and reference formulation, R, respectively. These hypotheses will be tested for the parameters AUC_{∞}, AUClast, and Cmax for the test formulation commercial tablets (Treatment C) vs the reference formulation T4 tablets (Treatment A). If the null hypotheses are

rejected for all 3 parameters then BE between Treatment A and Treatment C will be claimed. Then alpha (0.05) will be passed to test BE between the test formulation T3 mini-tablets (Treatment B) vs the reference formulation T4 tablets (Treatment A). If the null hypotheses are again rejected for all 3 parameters, then BE will be claimed for Treatment B and Treatment A.

A null hypothesis will be rejected if the 90% CI for GMR of the test and reference formulations is within 80.00% to 125.00% for the given parameter.

In the case that BE cannot be claimed between test Treatment C and reference Treatment A, there will be no hypotheses testing for BE between test Treatment B and reference Treatment A, even though the 90% CIs of GMRs for the given parameters between Treatment A and Treatment B will still be calculated.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

The overall type 1 error rate will be controlled using serial gatekeeping as described in Section 3.1. No multiplicity adjustments are planned.

4.0 SAMPLE-SIZE DETERMINATION

[redacted]

[redacted]

5.0 ANALYSIS SETS

5.1 Pharmacokinetic 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 set.

Details on criteria for excluding participants from the PK analysis will be described in the Clinical Pharmacology Analysis Plan (CPAP).

5.2 Safety Set

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

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonlin® Version 8.1, or higher. All statistical analyses will be conducted using SAS® Version 9.4 or higher. All data recorded on the case report form (CRF) will be listed by participant. All tables, figures, and listings (TFL) shells and numbering list will be included and specified in the TFL Shells document.

The number of observations (n) will be presented as an integer (no decimal places), arithmetic mean (mean), median, and geometric mean (Geom Mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic CV% and geometric percent coefficient of variation (Geom CV%) will be presented to 1 decimal place.

Geometric least-squares mean (LSMs) will be reported with 1 more level of precision than the individual data. GMRs and 90% CIs around the ratio will be reported to 2 decimal places, and intra-participant CV% will be reported to 1 decimal place.

Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and in the calculation of PK parameters, unless they are deemed questionable (eg, BLQ value between measurable values), in which case they will be treated as missing and excluded from the concentration summary statistics and the PK analysis.

A participant's PK parameter data will be included in the listings but may be excluded from the descriptive summary and statistical model if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that participant's maximum concentration value in that period.
- A participant did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).
- A participant deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist).
- Note: additional details for excluding subjects and/or PK parameters will be detailed in the CPAP.

The details on PK parameter calculations (individual PK parameters for each subject for each period) and TFLs will be outlined in the CPAP and TFL Shells document including specifics on the following:

[redacted]

- PK parameters presented by treatment for each study part, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables (CPAP and TFL Shells).
- Concentration data presented by treatment for each study part, including the units, precision, and summary statistics that will be presented in end-of-text tables (CPAP and TFL Shells).
- Concentration data file used for PK analysis (CPAP only).
- PK parameter WinNonlin® output file used to generate the TFLs (CPAP only).
- PK parameter ratios for C_{max}, AUC_{last}, AUC_{∞}, and AUC_{∞_pred} for each comparison of interest presented in end-of-text tables (CPAP and TFL Shells).
- Linear mixed-effects model results presented in in-text and end-of-text tables (CPAP and TFL Shells).

[redacted]

- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures (CPAP and TFL Shells).
- Individual concentration-time figures presented in Appendix 16.2.6 of the CSR (CPAP and TFL Shells).

Continuous demographic and safety data will be summarized descriptively by study part and time point, as applicable. For the categorical variables, the count and percentages of each possible value will be tabulated, where applicable. The denominator for the percent calculation will be the number of non-missing observations in the safety set by study part. Counts will be presented as integers. Percentages will be presented to one decimal. For continuous variables, n, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer.

Baseline, unless specified otherwise, is defined as the last observation prior to dosing in each period.

6.1.1 Handling of Treatment Misallocations

Participants who are misallocated treatments will be analyzed per the treatment they received rather than per the treatment regimen to which they were randomized.

6.2 Study Information

An overall study information table will be generated including the following items: date of first participant's signed informed consent form (ICF), date of first dose of study drug, date of last dose of study drug, date of last participant's last visit/contact, date of last participant's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets. Study drug refers to soticlestat.

6.3 Disposition of Participants

For each study part, disposition of participants (number of participants dosed, completed the study, discontinued from the study and/or study drug, and reason(s) for discontinuation(s)) will be summarized for each group by randomized treatment sequence and overall. Study completion status, including reason for discontinuation, will also be listed by participant.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized descriptively for each part by randomized treatment sequence and overall based on the safety set. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age, weight, height, and body mass index [BMI]) and the number and percentages of participants within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI measured at screening will be used in the summaries. Demographic data will also be listed as recorded on the CRF, including the date of informed consent and protocol version.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history to be recorded will include determining whether the participant has any significant conditions or diseases that resolved at or before signing the ICF. All medical history reported by the participant will be recorded regardless of how long ago it may have occurred. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each participant's medical history and concurrent medical conditions will be listed.

Any medical condition starting or worsening after taking the first dose of study drug will be classified as a TEAE. All medical history will be coded using MedDRA® version specified in the data management plan (DMP). All medical history and concurrent medical conditions will be listed. If available, the medical history and concurrent medical condition listings will include the coded term (preferred term [PT] and system organ class [SOC]), start date (if known) and end date (if known) or whether the condition was ongoing, and a description of the condition or event. No summaries or statistical analysis will be performed for these data.

6.5 Medication History and Concomitant Medications

Medication history to be obtained includes any medication stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between ICF and the end of the study (including follow-up contact). All medication history and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Drug Dictionary version specified in the DMP and listed. If available, the listings will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time (if known), or whether it continued after study completion, and indication for use. No summaries or statistical analysis will be performed for these data.

6.6 Efficacy Analysis

Not applicable.

6.7 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and relationship of TEAEs, C-SSRS, and changes from baseline in the participants' clinical laboratory results, vital signs, and 12-lead ECGs using the safety set. Clinically significant laboratory values, vital signs, and ECGs will be reported as AEs. All clinical safety data will be listed by study part, participant, and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically. Participants from each part will be included in the same listing but will be delineated by study part.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where

individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

6.7.1 Adverse Events

All AEs captured in the database will be listed in by-participant data listings including verbatim term, coded term, severity (mild, moderate, severe), relationship to study drug (related or not related), relationship to COVID-19 or COVID-19 vaccine, frequency, and action relative to the study drug as recorded in the CRF. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA® version specified in the DMP. Only TEAEs will be summarized.

A TEAE is defined as an AE that is starting or worsening from the first dose of study drug administered in the study. Each TEAE will be attributed to the treatment prior to and the closest to the AE based on the AE onset date and time.

If the onset time of an AE is missing and the onset date is the same as a treatment dosing date, then the AE will be counted under the treatment given on the same day. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment emergent for the most recent treatment administered. If the onset date of an AE is missing, then the AE will be considered treatment emergent and attributed to the first treatment received. If severity is missing, the AE will be counted under the highest severity, and if relationship is missing, the AE will be counted as related. Any medical condition starting or worsening after the ICF but before the first dose of study drug will be classified as pre-treatment event.

Summary of TEAEs will be presented for each study part. TEAEs will be tabulated by treatment (including overall), SOC, and PT. Summary tables will include number of participants reporting the TEAE and as percent of safety set by treatment and overall. The most commonly reported non-serious TEAEs (ie, those events reported by >5% of participants or >2 participants, whichever is larger overall, excluding serious adverse events (SAEs)) will also be summarized. The denominators for percent calculations will be the number of participants dosed for each treatment. In addition, TEAEs will be summarized as number of TEAEs and percentage of TEAEs for each treatment and overall.

Additional TEAE summary tables will be presented by severity and relationship to study drug. If a participant has multiple TEAEs with different severity levels within the same PT, the participant will be counted in the most severe category only. If a participant has both related and unrelated TEAEs with the same term, the participant will be counted as having related TEAEs.

An overview summary of TEAEs table, including number of participants with TEAEs, SAEs, treatment-related TEAEs, treatment-related SAEs, TEAEs by severity, and AEs leading to discontinuation of study drug will be provided.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAEs. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the CSR.

6.7.2 Adverse Events of Special Interest (if applicable)

Not applicable.

6.7.3 Clinical Laboratory Evaluation

Serum chemistry, hematology, coagulation, and urinalysis will be performed at the following time points in both parts: screening, Period 1 Day -1, Period 1 Day 4, Period 2 Day 4, and Period 3 Day 5 (or at early termination if applicable).

Urine drug screening will be carried out at screening and Period 1 Day -1 only, in both study parts. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for laboratory test results and change from baseline by treatment and time point of collection for each study part. Baseline is defined as the last assessment including rechecks taken prior to dosing in each period. For Periods 2 and 3 baseline, the Day 4 result from the previous period will be used. Postdose unscheduled or recheck assessments will not be used in analysis. All clinical laboratory data will be listed by study part and participant.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

6.7.4 Vital Signs

Vital sign measurements of pulse rate, blood pressure, respiration rate, and temperature will be obtained at the following time points in both parts: screening, Period 3 Day 5 (or at early termination if applicable), and the following time points in all 3 periods, Day 1 predose, Day 1 Hours 0.5 and 1.5, and Day 2.

Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the Investigator.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for vital sign results and change from baseline by treatment and time point of collection for each study part. Baseline is defined as the last assessment including rechecks taken prior to dosing in each

period. Postdose unscheduled or recheck assessments will not be used in analysis. Vital sign data will be listed by study part and participant.

6.7.5 12-Lead Electrocardiogram

Single 12-lead ECGs will be collected at the following time points in both parts: screening, Period 3 Day 5 (or at early termination if applicable), and the following time points in all 3 periods, Day 1 predose, Day 1 Hours 0.5 and 1.5, and Day 2.

Additional unscheduled ECGs may be taken at other times, if deemed necessary by the Investigator.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from study baseline by treatment and time point of collection for each study part. Baseline is defined as the last assessment including rechecks taken prior to dosing in each period. Postdose unscheduled or recheck assessments will not be used in analysis. ECG data will also be listed by study part and participant.

In addition, for each study part, frequency counts of worst post baseline QTcF, and worst change-from-baseline QTcF (ΔQTcF) will be presented by treatment. Number of participants and corresponding percentages will be presented for each category. Worst post baseline QTcF will be categorized in the following categories: <450, 450 – <480, 480 – 500, and >500. Worst post baseline ΔQTcF (maximum change from baseline) will be categorized in the following categories: <30, 30 – 60, and >60. A participant will be counted only once in each treatment even if the participant has more than 1 episode of the worst value.

6.7.6 Physical Examination

In both study parts, physical examinations will be performed at screening, Period 1 Day -1, Period 1 Day 4, Period 2 Day 4, and Period 3 Day 5 (or at early termination if applicable). Physical examination findings will be presented in the data listings by part and participant.

6.7.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

At screening for each study part, the C-SSRS Baseline/Screening version will be administered. On Period 1 Day -1 and Period 3 Day 5 (or at early termination, if applicable) of each study part, the 'Since Last Visit' version will be administered. C-SSRS findings will be presented in the data listings by part and participant.

6.7.8 Overdose

All cases of overdose will be presented in a data listing by study part and participant. Any AEs associated with overdose will be documented.

6.7.9 Extent of Exposure and Compliance

The date, time, and treatment will be listed by part and participant.

6.8 Pharmacokinetic Analysis

Blood samples for assessment of plasma soticlestat [redacted] concentrations will be collected as outlined in Table 6.a for Part A and in Table 6.b for Part B:

Table 6.a Collection of Blood Samples for Pharmacokinetic Analysis in Part A

Analytes	Matrix	Periods	Scheduled Time (Hours)[#]
Soticlestat [redacted]	Plasma	1, 2, and 3	Predose and 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96[*] hours postdose

[#] The actual date and time of sample collection will be recorded on the source document in the CRF.
[*] The 96-hour PK sample in Periods 1 and 2 will serve as the predose PK sample of Periods 2 and 3, respectively.

Table 6.b Collection of Blood Samples for Pharmacokinetic Analysis in Part B

Analytes	Matrix	Periods	Scheduled Time (Hours)[#]
Soticlestat [redacted]	Plasma	1, 2, and 3	Predose and 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96[*] hours postdose

[#] The actual date and time of sample collection will be recorded on the source document in the CRF.
[*] The 96-hour PK sample in Periods 1 and 2 will serve as the predose PK sample of Periods 2 and 3, respectively.

Concentrations of plasma soticlestat [redacted] at each sampling time will be listed and summarized descriptively by treatment for each study part using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, and maximum. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive statistics.

Individual participant concentration-time curves will be plotted by treatment for each study part on linear and semi-log scales. The arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales for each study part. For arithmetic mean concentration-time plots, the nominal PK sampling times will be used. For individual participant concentration-time plots, the actual PK sampling times will be used.

The PK parameters will be calculated from plasma soticlestat [redacted] concentration-time profiles using non-compartmental analysis methods where all calculations will be based on actual sampling times after soticlestat dosing. The PK parameters will be summarized by treatment for each study part using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, geom mean, and geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

Linear Mixed-Effects Model

For each study part, ln-transformed C_{max}, AUC_{last}, AUC_{∞}, and AUC_{∞_pred} 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}, AUC_{∞}, and AUC_{∞_pred} 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}, AUC_{∞}, and AUC_{∞_pred}.

[redacted]

The comparisons of interest are as follows:

BE (Part A)*:*

- *Treatment C compared with Treatment A*
- *Treatment B compared with Treatment A*

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 C_{max}, AUC_{last}, and AUC_{∞} 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 C_{max}, AUC_{last}, or AUC_{∞} GMRs 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%.

Food effect (Part B):

- *Treatment E compared with Treatment D*

Tablet crushing (Part B):

- *Treatment F compared with Treatment D*

The model will be run separately by study part, and using data for each analyte, as appropriate. The following SAS® code will be used to perform the analysis:

```
PROC MIXED DATA=xxx;
CLASS TREAT PERIOD SEQUENCE PARTICIPANT;
MODEL LN_PARAM = TREAT PERIOD SEQUENCE / DDFM=KR;
RANDOM PARTICIPANT(SEQUENCE);
ESTIMATE “Treatment C vs. Treatment A” TREAT -1 0 1 / CL ALPHA=0.1 E;
ESTIMATE “Treatment B vs. Treatment A” TREAT -1 1 0 / CL ALPHA=0.1 E;
LSMEANS TREAT;
RUN;
```

Programming note: For Part B the following estimate statements will be used:

ESTIMATE "Treatment E vs. Treatment D" TREAT -1 1 0 / CL ALPHA=0.1 E;
ESTIMATE "Treatment F vs. Treatment D" TREAT -1 0 1 / CL ALPHA=0.1 E;

[redacted]

6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.10 Preliminary Analyses

Preliminary PK analyses will be completed as described in the CPAP and Section 6.8 of the SAP, with the following changes: 1) QCed data will be used (not QAed); 2) nominal times (not actual sampling times) will be used for the calculation of PK parameters; and 3) tables and figures will be created using Phoenix® WinNonlin® Version 8.1 or higher, except for the tables presenting the linear mixed-effects model data which will be generated using SAS® Version 9.4 or higher.

6.11 Interim Analyses

Not applicable.

6.12 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The AUC_{∞_pred}, $AUC_{extrap}\%_{\_pred}$, $CL/F_{\_pred}$, $V_z/F_{\_pred}$, [redacted] will be presented as additional endpoints.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Analysis Software

SAS® Version 9.4 or higher will be used for all statistical analyses provided in the CSR.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	22-Mar-2022 17:54 UTC