**Statistical Analysis Plan**

NCT Number: NCT05098041

Title: Phase 1 Open-Label Study to Evaluate the Drug-Drug Interaction of Rifampin as a Strong CYP3A Inducer on Soticlestat Pharmacokinetics in Healthy Adult Participants

Study Number: TAK-935-1009

Document Version and Date: Final / 16-Nov-2021

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

# STATISTICAL ANALYSIS PLAN

Study Number: TAK-935-1009
Celerion Study Number: CA34934

A Phase 1 Open-Label Study to Evaluate the Drug-Drug Interaction of Rifampin as a Strong CYP3A Inducer on Soticlestat Pharmacokinetics in Healthy Adult Participants

Phase 1

Version: Final

Date: 16-Nov-2021

Prepared by:

[redacted]

Based on:

Protocol Version: Original

Protocol Date: 20-Aug-2021

## REVISION HISTORY

| Version | Approval Date | Primary Rationale for Revision |
|---|---|---|
| Original version | 16-Nov-2021 | Not Applicable |

## Approval Signatures

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

**Study Title:** A Phase 1 Open-Label Study to Evaluate the Drug-Drug Interaction of Rifampin as a Strong CYP3A Inducer on Soticlestat Pharmacokinetics in Healthy Adult Participants

**Approvals:**

Signatur [redacted]

## TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| $AUC_{\infty}$ | area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration. |
| $AUC_{extrap}\%$ | area under the curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of $AUC_{\infty}$. |
| $AUC_{last}$ | area under the concentration-time curve from time 0 to the time of the last quantifiable concentration |
| BLQ | below the lower limit of quantitation |
| BMI | body mass index |
| CI | confidence interval |
| CL/F | apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration. |
| $C_{max}$ | maximum observed concentration |
| COVID-19 | coronavirus disease 19 |
| 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% | arithmetic percent coefficient of variation |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| DMP | data management plan |
| ECG | electrocardiogram |
| Geom CV% | geometric percent coefficient of variation |
| Geom Mean | geometric mean |
| GMR | geometric least-squares mean ratio |
| LSM | least-squares mean |
| Mean | arithmetic mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| n | number of observations |
| PK | pharmacokinetic |
| PRO | patient-reported outcome |
| PT | preferred term |
| QD | once daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SEM | standard error of the mean |
| SOC | system organ class |

| | |
|---|---|
| $t_{1/2z}$ | terminal disposition phase half-life |
| TAK-935 | soticlestat |
| [redacted] | [redacted] |
| TEAE | treatment-emergent adverse event |
| TFL | table, figure, and listing |
| $t_{max}$ | time of first occurrence of $C_{max}$ |
| $V_z/F$ | apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration. |
| WHO | World Health Organization |
| $\lambda_z$ | terminal disposition phase rate constant |

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, $AUC_\infty$ and $\lambda_z$ will be presented as AUCinf and Lambdaz in the end-of-text tables, respectively.

# 1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

## 1.1 Objectives

### 1.1.1 Primary Objective

*To characterize the effect of rifampin, a strong CYP3A inducer, on the single-dose pharmacokinetics (PK) of soticlestat.*

### 1.1.2 Secondary Objective

*To assess the safety and tolerability of soticlestat following a single oral dose in healthy adult participants with/without a strong CYP3A inducer.*

[redacted]

## 1.2 Endpoints

### 1.2.1 Primary Endpoints

*The following PK parameters will be analyzed for soticlestat, when administered alone and when co-administered with rifampin:*

- *Maximum observed concentration ($C_{max}$).*
- *Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration ($AUC_{\infty}$).*
- *Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{last}$).*
- *Time of first occurrence of $C_{max}$ ($t_{max}$).*

### 1.2.2 Secondary Endpoints

- *Number of participants with at least one treatment-emergent adverse event (TEAE).*
- *Incidence of clinically significant abnormal values for laboratory evaluations, vital signs, electrocardiogram (ECG) parameters, and Columbia-Suicide Severity Rating Scale (C-SSRS).*

### 1.3 Estimand(s)

Not applicable.

## 2.0 STUDY DESIGN

*This is an open-label, 2-period, fixed-sequence drug-drug interaction (DDI) study to evaluate the effect of a strong CYP3A inducer, rifampin, on the single-dose PK of soticlestat in healthy participants.*

*Study schematics of the study design and dose regimens are shown in Table 2.a and Table 2.b, respectively.*

### *Table 2.a Study Schematic*

| | *Period 1* | | | *Period 2* | | | |
|---|---|---|---|---|---|---|---|
| *Screening* | *Check-in and Predose Assessments* | *Soticlestat Dosing, PK Sampling, and Study Assessments* | *PK Sampling and Study Assessments* | *Rifampin Dosing and Study Assessments* | *Co-administration (Rifampin and Soticlestat), PK Sampling, and Study Assessments* | *Rifampin Dosing, PK Sampling and Study Assessments* | *Follow-up* |
| *Within 28 days prior to first dosing* | *Day -1* | *Day 1* | *Day 2-5[a]* | *Day 1[a]-10* | *Day 11* | *Day 12 -14[c]* | *15 (± 2) days following last soticlestat dose* |
| | *----------Confinement[b]----------* | | | | | | *Contact* |

[a] *Day 5 Period 1 will also be considered Day 1 Period 2.*
[b] *Participants will start the confinement on Day -1 Period 1 and will remain confined until Day 14 Period 2.*
[c] *Last dose of rifampin will be administered on Day 13.*

### *Table 2.b Dose Regimens for Study Drugs*

| *Study Drug* | *Dose* | *Dose Regimen* | *Number of Days on Study Drug* |
|---|---|---|---|
| *Soticlestat (T4 tablets)* | *300 mg (3 x 100 mg tablets)* | *Single dose, oral* | *Day 1 Period 1 and Day 11 Period 2* |
| *Rifampin (capsules)* | *600 mg (2 x 300 mg capsules)* | *QD, oral* | *Days 1 through 13 Period 2* |

*Participants will be screened within 4 weeks (28 days) prior to the first administration of soticlestat (Day -28 to first dosing, Day 1). Qualified participants will be admitted to the clinic on Day -1 of Period 1, at the time indicated by the clinical research unit (CRU), and will remain confined until after the last blood draw and/or study procedures on Day 14 of Period 2.*

*In Period 1, on Day 1, participants will receive a single dose of soticlestat (300 mg; 3 x 100 mg T4 tablets) under fasting conditions. 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 4 days between the soticlestat dose in Period 1 and the first rifampin dose in Period 2.*

*In Period 2, from Days 1 to 13, participants will receive a QD oral dose of rifampin (600 mg; 2 x 300 mg capsules) under fasting conditions. On the morning of Day 11, participants will receive a single dose of soticlestat (300 mg; 3 x 100 mg T4 tablets) co-administered with the rifampin dose under fasting conditions. Blood samples for the PK of soticlestat [redacted] will be collected at scheduled time points from soticlestat predose on Day 11 through 72 hours postdose.*

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

*After discharge, the CRU will contact all participants (including participants who terminate the study early) 15 (± 2) days after the last soticlestat administration by telephone or other methods per CRU standards to determine if any AE has occurred or 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.*

## 3.0 STATISTICAL HYPOTHESES AND DECISION RULES

### 3.1 Statistical Hypotheses

Not applicable.

### 3.2 Statistical Decision Rules

Not applicable.

### 3.3 Multiplicity Adjustment

Not applicable.

## 4.0 SAMPLE-SIZE DETERMINATION

*This study is not powered for hypothesis testing and is not based on any specific no-effect boundaries. The sample size is based on an estimation approach and is considered sufficient to provide a reliable estimate of the DDI magnitude.*

[redacted]

*A total of 14 participants will be dosed to ensure that 12 evaluable subjects complete the study.*

# 5.0 ANALYSIS SETS

## 5.1 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 set.*

## 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 percent coefficient of variation (CV%) and geometric percent coefficient of variation (Geom CV%) will be presented to 1 decimal place.

Geometric least-squares means (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 (e.g., 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).

The details on PK parameter calculations and TFLs will be outlined in the Clinical Pharmacology Analysis Plan (CPAP) and TFL Shells document including specifics on the following:

[redacted]

- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables.
- Concentration data file used for PK analysis.
- PK parameter WinNonlin® output file used to generate the TFLs.
- Linear mixed-effects model results presented in in-text and end-of-text tables.
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures.
- Individual concentration-time figures presented in Appendix 16.2.6 of the CSR.

Continuous demographic and safety data will be summarized descriptively by 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. Counts will be presented as integers. Percentages will be presented to one decimal. For continuous variables, the number of observations, 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 the first dose of the study.

### 6.1.1 Handling of Treatment Misallocations

Participants who are misallocated treatments will be analyzed per the treatment they actually received rather than per the treatment they were supposed to receive.

## 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 or rifampin.

## 6.3 Disposition of Participants

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 and listed by participant.

## 6.4 Demographic and Other Baseline Characteristics

### 6.4.1 Demographics

Demographic and baseline characteristics will be summarized 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). 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 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(s) of TEAEs, 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, ECGs, and C-SSRS results will be reported as AEs, as applicable. All safety data will be listed by participant and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

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(s) (related or not related), relationship to COVID-19 or COVID-19 vaccine, frequency, and action relative to the study drug(s) 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 at the time of or after 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 as described in Table 6.a.

**Table 6.a AE Treatment Assignment Algorithm**

| Date and Time of AE With Respect to Date and Time of Dosing | Treatment |
|---|---|
| Period 1 Day 1 soticlestat dosing ≤ Date and Time of AE < Period 2 Day 1 rifampin dosing | Soticlestat Alone |
| Period 2 Day 1 rifampin dosing ≤ Date and Time of AE < Period 2 Day 11 soticlestat dosing | Rifampin Alone |
| Period 2 Day 11 soticlestat dosing ≤ Date and Time of AE | Soticlestat + Rifampin |

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.

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 in any treatment (Soticlestat Alone, Rifampin Alone, or Soticlestat + Rifampin), 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(s). 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. For relationship to study drug(s), 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 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 screening, Period 1 Day -1, Period 1 Day 3, Period 2 Day 11 predose, and Period 2 Day 13 predose (or at early termination if applicable).

Urine drug screening will be carried out at screening and Period 1 Day -1 only. 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 at each scheduled visit. Baseline is defined as the last assessment including rechecks taken prior to the first dose in the study in Period 1. Postdose unscheduled or recheck assessments will not be used in analysis. All clinical laboratory data will be listed by 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 screening, Period 1 Day 1 predose, Period 1 Day 1 Hours 0.5 and 1.5, Period 1 Day 2, Period 2 Day 11 predose, Period 2 Day 11 Hours 0.5 and 1.5, Period 2 Day 12 predose, and Period 2 Day 14 (or at early termination if applicable). 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 at each study scheduled visit. Baseline is defined as the last assessment including rechecks taken prior to the first dose in the study in Period 1. Postdose unscheduled or recheck assessments will not be used in analysis. Vital sign data will be listed by participant.

### 6.7.5 12-Lead Electrocardiogram

Single 12-lead ECGs will be collected at screening, Period 1 Day 1 predose, Period 2 Day 11 predose, and Period 2 Day 14 (or at early termination if applicable). 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 time point of collection. Baseline is defined as the last assessment including rechecks taken prior to the first dose in the study in Period 1. Post-baseline unscheduled or recheck assessments will not be used in analysis. ECG data will also be listed by participant.

In addition, shifts from baseline to the worst post baseline QTcF, and shifts from baseline to the worst change-from-baseline QTcF (ΔQTcF) will be presented as cross tabulations (baseline versus post baseline values). Number of subjects and corresponding percentages will be presented for each category. For shifts from baseline to the worst post baseline QTcF, baseline values will be categorized in the following categories: < 450, 450 – < 480, 480 – 500, > 500, and missing; the worst post-baseline QTcF values will be categorized similarly. For shifts from baseline to the worst post baseline ΔQTcF, baseline values will be categorized in the following categories: < 450, 450 – < 480, 480 – 500, > 500, and missing; the maximum change from baseline values will be categorized into three categories: < 30, 30 – 60, and > 60. A subject will be counted only once even if the subject has more than 1 episode of the worst value.

### 6.7.6 Physical Examination

A full physical examination will be performed at screening and an abbreviated physical examination will be performed on Period 1 Day -1. Symptom-driven physical examinations may be performed at other times at the discretion of the Investigator. Physical examination findings will be presented in the data listings by participant.

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

At screening, the C-SSRS Baseline/Screening version will be administered. On Period 1 Day -1 and Period 2 Day 14 (or at early termination, if applicable), the 'Since Last Visit' version will be administered. C-SSRS findings will be presented in the data listings by participant.

### 6.7.8 Overdose

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

### 6.7.9 Extent of Exposure and Compliance

The date, time, and dose of single oral dose of soticlestat and multiple oral doses of rifampin will be listed by participant.

## 6.8 Pharmacokinetic Analysis

Blood samples for assessment of plasma soticlestat, [redacted] concentrations will be collected as outlined in Table 6.b below:

**Table 6.b Collection of Blood Samples for Pharmacokinetic Analysis**

| Analytes | Matrix | Period | Scheduled Time (Hours)* |
|---|---|---|---|
| Soticlestat, [redacted] | Plasma | 1 | Predose, and 0.133, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 14, 24, 36, 48, 72, and 96** hours post soticlestat dose. |
| | | 2 | Predose, and 0.133, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 14, 24, 36, 48, and 72 hours post soticlestat dose. |

*The actual dates and times of sample collection will be recorded on the source document in the CRF.
**Hour 96 in Period 1 will be predose of Period 2.

Concentrations of plasma soticlestat, [redacted] at each sampling time will be listed and summarized descriptively by treatment 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 on linear and semi-log scales. Arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales. 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 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***

*Ln-transformed soticlestat $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$ data will be analyzed using a linear mixed-effects model, separately. The model will include treatment (Soticlestat + Rifampin, Soticlestat Alone) as a fixed effect and participant as a random effect. The point estimates and 90% CIs for the GMRs of $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$ for Soticlestat + Rifampin versus Soticlestat Alone will be calculated using the exponentiation of the point estimates of the difference between treatment regimen and the corresponding 90% CIs from the analyses on the ln-transformed $C_{max}$, $AUC_{last}$, and $AUC_{\infty}$.*

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

```
PROC MIXED DATA=xxx;
CLASS TREAT PARTICIPANT;
MODEL LN_PARAM = TREAT / DDFM=KR;
RANDOM PARTICIPANT;
ESTIMATE "Soticlestat + Rifampin vs Soticlestat Alone" TREAT -1 1 / CL ALPHA=0.1 E;
LSMEANS TREAT;
RUN;
```

[redacted]

***Non-Parametric Analysis***

*Soticlestat $t_{max}$ will be analyzed using nonparametric analysis for paired samples (the Wilcoxon Signed Rank Test statistic). The difference of medians (treatment effect) and the corresponding 90% CI will be estimated using the Hodges-Lehmann method and Walsh Averages. $t_{max}$ will not be ln-transformed. The comparison of interest is the same as for the linear mixed-effects analysis above.*

[redacted].

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

Not applicable.

### 6.10 Interim Analyses

No interim analysis is planned for this study.

### 6.11 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.

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

Not applicable.

## 7.0 REFERENCES

Kupper, L. L. and Hafner, K.B., How appropriate are popular sample size formulas? Am Stat, 1989. 43(2): 101-105.

## 8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

The protocol indicates that C-SSRS results will be summarized by point of time of collection. Due to the nature of the questionnaire, these results will be listed but not summarized. C-SSRS responses of interest will be discussed in the CSR.

## 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 clinical study report.

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| [redacted] | Biostatistics Approval | 19-Nov-2021 16:28 UTC |