Statistical Analysis Plan

NCT Number: NCT05098054

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

Study Number: TAK-935-1010

Document Version and Date: Amendment 1; 12-Jul-2022

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-935-1010

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

Phase: 1

Version: Amendment 1

Date: 12-Jul-2022

Prepared by:

[redacted]

Based on:

Protocol Version: Amendment 1

Protocol Date: 11-Apr-2022

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	27-Oct-2021	Not Applicable
Amendment 1	12-Jul-2022	The severe hepatic impairment cohort was changed to a mild hepatic impairment cohort. All references to the severe cohort in this SAP have been changed to mild. Furthermore, the dose will not be adjusted and will stay at 300 mg. Other minor corrections were made from the previous version. No changes were made to statistical methods.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

ABBREVIATIONS

ΔQTcF	change-from-baseline QTcF
AE	adverse event
ANOVA	analysis of variance
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{last}	area under the concentration-time curve from time 0 to the time 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_{∞}
BLQ	below the lower limit of quantitation
BMI	body mass index
C-SSRS	Columbia suicide severity rating scale
CI	confidence interval
[redacted]	
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
CV%	coefficient of variation
ECG	electrocardiogram
ET	early termination
Geom mean	geometric mean
Geom CV%	geometric percent coefficient of variation
GMR	geometric mean ratio
HI	hepatic impairment
ICF	informed consent form
LSMs	least-squares means
MAV	markedly abnormal value
MedDRA®	Medical Dictionary for Regulatory Activities
[redacted]	
n	number of observations
PK	pharmacokinetic
PRO	patient-reported outcomes
PT	preferred term
QTcF	QT interval corrected for PR using Friderica's formula
SAE	serious adverse event
SAP	statistical analysis plan

SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{½z}$	Terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
[redacted]	
[redacted]	
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective

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

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint(s)

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

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

1.2.2 Secondary Endpoint(s)

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

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

[redacted]

1.3 Estimand(s)

Not applicable

2.0 STUDY DESIGN

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

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

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

Two hepatic function assessments are required prior to Day 1 dosing for participants with HI. These 2 assessments should be obtained during the screening period and at least 48 hours apart. In the case, where a participant has an available historical Child-Pugh assessment score within 3 months prior to screening, 1 assessment can be conducted during the screening period. If the Child-Pugh scores from these 2 assessments indicate the same liver function category for the participant (ie, normal hepatic function, moderate HI, or mild HI), soticlestat can be administered as scheduled. If the results of the 2 assessments indicate different liver function categories, a third assessment must be conducted at least 24 hours after the second assessment.

If the results of the 2 most recent assessments (the second and third) are in agreement with regard to the participant's liver function category, the participant may be enrolled and should receive the Day 1 dose within 48 hours of the third assessment. If the second and third measurements differ, the participant will not be eligible for the study.

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

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

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

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

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

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

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

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

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

5.2 Pharmacokinetic Analysis Set

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

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. All data recorded on the case report form (CRF) will be listed by hepatic function group and participant. All table, figure, and listing (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. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the GMRs will be reported using 2 decimal places.

Noncompartmental analyses will be used in this study. 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 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. Values of 0 are not included in the calculation of geom mean and geom CV%.

A participant's PK parameter data will be included in the listings but may be excluded from the descriptive and inferential (linear mixed-effects model) statistics if one or more of the following criteria are met:

- A predose (0 hour) concentration is greater than 5% of that participant's maximum concentration value for the given hepatic function group
- A participant did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda 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)
- A participant may be excluded due to vomiting

The details on PK parameter calculations and TFLs will be outlined in the clinical pharmacology and analysis plan (CPAP) and TFL Shells document including specifics on the following:

[redacted]

- For participants with AUC_{extrap}% greater than 20%, the descriptive and model-based statistics for AUC_{∞} will be presented with and without these participants included, if appropriate
- PK parameters presented by hepatic function group, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by hepatic function group, 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 Phoenix® WinNonlin® output file used to generate the TFLs
- ANOVA 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.

Fraction unbound will be calculated based on the ratios of unbound concentration relative to total concentration at 0.5 and 10 hours postdose for each subject as follows: $Fu_{0.5\ hrs} = Cu_{0.5\ hrs}/C_{0.5hrs}$ and $Fu_{10hrs} = Cu_{10hrs}/C_{10hrs}$ (where Cu_t = unbound concentration in plasma at time t and C_t = total concentration in plasma at time t).

Continuous demographic and safety data will be summarized descriptively. For 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 participants in the safety set for overall summaries, and the number of participants dosed in each hepatic function group in hepatic function group summaries. 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. Counts and percentages will be presented to 1 decimal place. Baseline is defined as the last observation prior to dosing.

If additional normal hepatic function participants are added to match the mild HI group due to differences in matching criteria, then disposition and demographic summaries for the normal hepatic function group may be separated based on matching to moderate HI or mild HI.

6.1.1 Handling of Treatment Misallocations

Not applicable

6.2 Study Information

A study information table will be generated including the following items: date of first participant's signed informed consent form, date of dosing, 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) Drug Dictionary, and SAS version used for creating the datasets.

6.3 Disposition of Participants

Disposition of participants (number of participants dosed, completed the study, discontinued from the study, discontinued from the study drug, and reason(s) for discontinuation(s)) will be summarized by matched hepatic function group (ie, Severe HI, Moderate HI, Mild HI, Normal Hepatic Function (Mild), Normal Hepatic Function (Moderate), Normal Hepatic Function (Overall)) and overall. Study completion status, including reason for discontinuation, will also be listed by hepatic function group and participant.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized descriptively matched hepatic function group (ie, Severe HI, Moderate HI, Mild HI, Normal Hepatic Function (Mild), Normal Hepatic Function (Moderate), Normal Hepatic Function (Overall)) and overall. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age as collected on CRF, weight, height, and BMI) and the number and percentage of participants within each category will be presented for categorical variables (sex, race, and ethnicity). The last height, weight, and BMI recorded prior to dosing will be used in the baseline summaries. Demographics data will also be listed as recorded in the case report form (CRF), including the date of informed consent.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history will include determining whether the participant has any significant conditions or diseases that resolved at or before signing the informed consent form (ICF). 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 started after taking the study drug will be classified as an adverse event. All medical history will be coded using the MedDRA® Version 24.1. The medical history listing will include the system or organ class (SOC) involved, preferred term (PT), start date (if known) and end date (if known) or whether the condition was ongoing, and a description of the condition or event. There will be no analysis of medical history.

6.4.3 Baseline Characteristics

Child-Pugh scores will be assessed at screening to classify participants into hepatic function groups. Two hepatic function assessments are required prior to Day 1 for participants with HI. These 2 assessments should be obtained during screening and at least 48 hours apart. In the case where a participant has an available historical Child-Pugh assessment score within 3 months prior to screening, 1 assessment can be conducted during the screening period. If the results of the 2 assessments indicate different liver function categories, a third assessment must be conducted at least 24 hours after the second assessment. The last recorded scores will be summarized (n, mean, SD, minimum, median, and maximum) by hepatic function group and presented in the demographic summary table. Individual results will be listed by hepatic function group and participant.

6.5 Medication History and Concomitant Medications

Medication history will include any medication relevant to eligibility criteria and safety evaluation 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 visit). All medication history and concomitant medications recorded

during the study will be coded with the WHO Global Dictionary September 2021 and listed. If appropriate, the listing will include the medication name, coded term, dosage, route of administration, start date and end date, or whether it continued after study completion, and indication for use. There will be no statistical analysis of medication history or concomitant medications.

6.6 Efficacy Analysis

Not applicable

6.7 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and relationship 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 CSSRS results will be reported as AEs. All safety data will be listed by hepatic function group (ie, Severe HI, Moderate HI, Mild HI, Normal Hepatic Function), participant, and assessment time points, including rechecks, unscheduled assessments, and early termination (ET) assessments, 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. If additional normal hepatic function participants are added to match the mild HI group, then the normal hepatic function group will be separated based on matching to moderate HI or mild HI.

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), frequency, and action relative to the study drug as recorded in the CRF. All AEs occurring during this study will be coded using the MedDRA® Version 24.1. Only TEAEs will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after dosing of study drug.

If the onset time of an AE is missing and the onset date is the same as the dosing date, then the AE will be counted as treatment-emergent. If the onset date of an AE is missing, then the AE will be considered treatment-emergent, unless the AE is known to have started prior to dosing. If severity is missing, the AE will be counted as severe, and if relationship is missing, the AE will be counted as related.

TEAEs will be tabulated by hepatic function group (ie, Severe HI, Moderate HI, Mild HI, Normal Hepatic Function), SOC, and PT. Summary tables will include the number and percent of participants reporting the TEAE by hepatic function group. In addition, the number and

percent of TEAEs for each hepatic function group will be summarized. Tables for the most commonly reported non-serious TEAEs (ie, those events reported by >1 participant in one or more hepatic function groups, and TEAEs that are >5% of total TEAEs (or >1 event if fewer than 20 TEAEs), excluding serious adverse events (SAEs)) and for SAEs only, will also be presented. The denominators for percent calculations will be the number of participants dosed or number of events for each hepatic function group.

Additional TEAE summary tables for participants and events will be presented by severity and relationship to study drug. If a participant experiences the same TEAE at more than one level of severity, the participant will be counted in the most severe category only. For relationship to study drug, if a participant has both related and unrelated TEAEs with the same term, the participant will be counted in the related category.

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

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

6.7.2 Adverse Events of Special Interest (if applicable)

Not applicable

6.7.3 Clinical Laboratory Assessments

Hematology, serum chemistry, coagulation, and urinalysis will be performed at screening, Day -1, Day 3, and Day 7 (or at ET if applicable). Urine drug screening will be carried out at screening and Day-1 only. For female participants, a pregnancy test will be performed at screening and check-in and FSH will be checked at screening. 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 each laboratory test by hepatic function group (ie, Severe HI, Moderate HI, Mild HI, Normal Hepatic Function) and time point of collection. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including recheck and unscheduled assessments, taken prior to dosing. All clinical laboratory listings and tables will be presented in international system (SI) units. Postdose unscheduled or recheck assessments will not be used in analysis. Similarly, ET results will not be included in summaries.

For calculation of summary statistics, lab results below or equal to lower limit of quantification (LLOQ) will be set to LLOQ/2 if a LLOQ value has been defined, and otherwise will be set to missing; lab results above or equal to upper limit of quantification (ULOQ) will be set to ULOQ

if a ULOQ value has been defined, and otherwise will be set to missing. Listings will display the original result received from the laboratory.

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 consist of temperature, respiratory rate, blood pressure (BP), and heart rate (HR). BP and HR will be collected at screening, within 24 hours prior to dosing on Day 1, and at 2, 24, and 144 hours postdose (or at ET if applicable). Respiratory rate and temperature will be recorded at screening, within 24 hours prior to dosing on Day 1, and at 24 and 144 hours postdose (or at ET if applicable). Additional unscheduled vital signs may be recorded at other times if deemed necessary by the Investigator.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital signs results by hepatic function group (ie, Severe HI, Moderate HI, Mild HI, Normal Hepatic Function) and time point of collection. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including recheck and unscheduled assessments, taken prior to dosing. Postdose unscheduled or recheck assessments will not be used in analysis. Similarly, ET results will not be included in summaries. Vital sign data will also be displayed in a data listing by hepatic function group and participant.

6.7.5 Electrocardiograms

Single 12-lead ECGs will be collected at screening, within 24 hours prior to dosing on Day 1, and at 2, 24, and 144 hours postdose (or at ET if applicable). Additional unscheduled ECGs may be recorded at other times if deemed necessary by the Investigator.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results by hepatic function group (ie, Severe HI, Moderate HI, Mild HI, Normal Hepatic Function) and time point of collection. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment, including recheck and unscheduled assessments, taken prior to dosing. Postdose unscheduled or recheck assessments will not be used in analysis. Similarly, ET results will not be included in summaries. ECG data will also be displayed in a data listing by hepatic function group and participant.

Shifts from baseline to the worst post baseline QT interval corrected for PR using Friderica's formula (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 the following categories: < 30, 30 – 60, > 60, and Missing. A subject will be counted only once even if the subjects has more than 1 episode of the worst value.

6.7.6 Physical Examination

Full physical examinations will be performed at screening, Day -1, and Day 7 (or ET if applicable). If the screening assessment was conducted within 4-7 days prior to dosing (Day 1), assessment will be conducted at Day -1 only if, in the opinion of the Investigator or designee, there is reason to believe they have substantially changed. Symptom-driven physical exams may be performed at other times at the discretion of the Investigator. Physical exam findings will be presented in the data listings by hepatic function group and participant.

6.7.7 Overdose

All cases of overdose will be presented in a data listing by participant.

6.7.8 Columbia Suicide Severity Rating Scale (C-SSRS)

At screening, the C-SSRS Baseline/Screening version will be administered. On Day -1 and Day 7 (or at ET, if applicable), the 'Since Last Visit' version will be administered.
C-SSRS findings will be presented in the data listings by participant.

6.7.9 Extent of Exposure and Compliance

The date, time, and treatment administered will be listed by hepatic function group and participant.

6.8 Pharmacokinetic Analysis

Blood samples for assessment of plasma soticlestat (TAK-935), [redacted] concentrations will be collected as outlined in Table 6.a below:

Table 6.a Collection of Blood Samples for Pharmacokinetic Analysis

Analytes	Matrix	Day	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, 96, 120, and 144 hours postdose.
[redacted]	Plasma	1	Predose, 0.5, and 10 hours postdose.

*The actual date and time of sample collection will be recorded on the source document in the case report form.
Note: The collection time points are relative to soticlestat dosing on Day 1.

Plasma concentrations of soticlestat (total and unbound), [redacted] will be listed and summarized descriptively by PK sampling time according to hepatic function group (normal hepatic function and moderate and mild HI) 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 hepatic function group on linear and semi-log scales. The mean profiles of the concentration-time data will be plotted by hepatic function group on linear (with and without SD) and semi-log scales. For summary statistics and mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

The PK parameters will be calculated from soticlestat (total and unbound), [redacted] concentration-time profiles using non-compartmental analysis methods where all calculations will be based on actual sampling times after dosing. The PK parameters will be summarized, defined in the CPAP, according to hepatic function group (normal hepatic function and moderate and mild HI) using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, geom mean (C_{max}, AUC_{∞}, and AUC_{last} only), and geom CV% (C_{max}, AUC_{∞}, and AUC_{last} only). Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

Individual plasma soticlestat (total and unbound), [redacted] AUC_{∞} values for participants with moderate and mild hepatic impairment as well as healthy participants will be plotted versus serum alpha-1-acid glycoprotein, serum albumin, total serum bilirubin, and INR ratio. In addition, individual plasma soticlestat (total and unbound), [redacted] AUC_{∞} values will be plotted versus Child-Pugh scores in participants with moderate and mild hepatic impairment.

Analysis of Variance (ANOVA)

An ANOVA will be performed on the ln-transformed C_{max}, AUC_{last}, and AUC_{∞} for total soticlestat, [redacted] to compare each HI group (moderate HI and mild HI) with the normal matched hepatic function group, where 90% CIs for the ratio of GMRs from each HI group versus normal matched function group will be provided. For total [redacted] an ANOVA will also be performed on the ln-transformed PK parameters for MRC_{max}, $MRAUC_{last}$, and $MRAUC_{\infty}$. The addition of other factors and covariates such as age, sex, and BMI on the relationship between soticlestat PK parameters and level of HI may also be investigated.

The ANOVA model will include hepatic function (Moderate HI, Mild HI, Normal Matched Hepatic Function) group as a fixed effect. GMRs and 90% CIs will be calculated from the exponentiated difference between group least squares means and corresponding 90% CIs from the analyses on the ln-transformed C_{max}, AUC_{last}, AUC_{∞}, MRC_{max}, $MRAUC_{last}$, and $MRAUC_{\infty}$. The GMRs and 90% CIs will be expressed as a percentage relative to the Normal Hepatic Function group.

The above statistical analyses will also be performed on the ln-transformed $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$ for unbound soticlestat.

If all subjects in the healthy group are matched to both the moderate HI and mild HI groups, the ANOVA analysis will be performed using the following SAS® code. Note that due to expected differences in the variability of PK parameter values between groups, the residual variance will be estimated separately for each group with use of the repeated statement, and variance components as the covariance matrix structure:

[redacted]

Where 'Arm' is as described in Section 2.0 where 1=Moderate HI, 2=Mild HI, 3=Normal Function. Appropriate coefficients will be used based on the input variable for arm.

If 2 healthy groups are needed to match moderate HI and mild HI separately due to differences in matching criteria, the analysis will be performed as follows:

Moderate HI versus matched Normal Function

The data will be subset to contain the moderate HI group and the matched normal function group. The ANOVA analysis will then be performed using the following SAS® code:

[redacted]

Appropriate coefficients will be used based on the input variable for arm.

Mild HI versus matched Normal Function

The data will be subset to contain the mild HI group and the matched normal function group. The ANOVA analysis will then be performed using the following SAS® code:

[redacted]

[redacted]

Appropriate coefficients will be used based on the input variable for arm.

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

Not applicable

6.10 Preliminary Analysis

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

This amendment was written following the preliminary analysis. The preliminary analysis indicated higher impact of moderate HI on soticlestat PK than predicted based on model-based stimulations. The Sponsor decided to remove the participants with severe HI from the study because soticlestat will not be recommended to use in subjects with severe HI. The amendment is created to evaluate the impact of mild HI on the PK of soticlestat.

6.11 Interim Analysis

No interim analysis is planned for this study.

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

Description as in protocol	Change	Rationale for Change
Incidence of clinically significant abnormal values for laboratory evaluations,	The analysis will not be performed.	This endpoint is included as part of standard AE reporting and will not be analyzed separately.

Description as in protocol	Change	Rationale for Change
vital signs, ECG parameters, and C-SSRS		
Vital signs assessments will be summarized by group and point of time of collection and a shift table describing out of normal range shifts will be provided.	A shift table will not be generated for vital signs	The normal criteria are not defined, and analysis of out of normal range shifts is not required.
C-SSRS results will be summarized by group and point of time of collection and a shift table describing out of normal range shifts will be provided	C-SSRS data will not be summarized	Normal criteria are not defined, and summary is not required. Data will be listed and discussed in the CSR.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Changes made from the previous version of the SAP that have a **material impact to the planned statistical analysis methods** are described below. In addition, there were textual changes purely to improve the flow, organization and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
All	All instances of **severe**	Changed to **mild**	Per protocol amendment, the severe hepatic impairment cohort was changed to a mild hepatic impairment cohort. All references to the severe cohort in this SAP have been changed to mild.

9.2 Data Handling Conventions

Not applicable

9.3 Analysis Software

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	13-Jul-2022 14:18 UTC