Title: A Phase 1, Open-Label Study to Evaluate the Effect of Itraconazole and Mefenamic Acid on the Single-Dose Pharmacokinetic Profile of Soticlestat in Healthy Participants

NCT Number: NCT05064449

SAP Approve Date: 15 October 2021

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-935-1007
Celerion Study Number: CA33003

A Phase 1, Open-Label Study to Evaluate the Effect of Itraconazole and Mefenamic Acid on the Single-Dose Pharmacokinetic Profile of Soticlestat in Healthy Participants

Phase 1

Version: Final

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Prepared by:

PPD

Based on:

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Protocol Date: 23-Aug-2021

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
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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 Effect of Itraconazole and Mefenamic Acid on the Single-Dose Pharmacokinetic Profile of Soticlestat in Healthy Participants

Approvals:

Signature:

PPD

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AEs	adverse events
AUC_{∞}	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_{∞}.
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
CI	confidence interval
CCI	[redacted]
C_{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	arithmetic percent coefficient of variation
DDI	drug-drug interaction
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
PBPK	physiologically-based pharmacokinetics
PK	pharmacokinetic
PROs	patient-reported outcomes
Q6H	every 6 hours
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
CCI	[redacted]
TAK-935	soticlestat
CCI	[redacted]
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time of first occurrence of C_{max}

CCI

CCI

Note: The PK parameters presented in the clinical study report 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_{∞} and C[redacted] ill be presented as AUCinf CCI in the end-of-text tables, respectively.

CCI

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

- *Part 1: To assess the effect of multiple-dose administration of itraconazole, a strong CYP3A inhibitor, on the single-dose pharmacokinetics (PK) of soticlestat.*
- *Part 2: To assess the effect of multiple-dose administration of mefenamic acid, a strong UGT1A9 inhibitor, on the single-dose PK of soticlestat.*

1.1.2 Secondary Objective

- *Part 1 and Part 2: To evaluate the safety and tolerability of soticlestat following a single oral dose in healthy adult participants with/without strong CYP3A and UGT1A9 inhibitors.*

CCI [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 itraconazole (Part 1) or mefenamic acid (Part 2):

- *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})*
- *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)*

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[redacted]

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a 2 part, open-label, drug-drug interaction (DDI) study to evaluate the effect of a strong CYP3A inhibitor, itraconazole (Part 1), and a strong UGT1A9 inhibitor, mefenamic acid (Part 2), on the single-dose PK of soticlestat in healthy adult participants.

Each part will be conducted independently as a 2-period, fixed-sequence design. Study schematics of the study design and dose regimen are shown in Table 2.a, Table 2.b, Table 2.c, and Table 2.d.

Table 2.a Study Design for Part 1

S	*Period 1*			*Period 2*				*FU*
	C-I and Predose Assessments	*Soticlestat Dosing, PK Sampling and Study Assessments*	*PK Sampling and Study Assessments*	*Itraconazole Dosing and Study Assessments*	*Co-administration (Itraconazole and Soticlestat), PK Sampling and Study Assessments*	*Itraconazole Dosing, PK Sampling and Study Assessments*	*Study Exit [c] (PK Samping and Study Assessments)*	
Within 28 days prior to first dosing	*Day -1*	*Day 1*	*Day 2 – 5 [a]*	*Day 1 [a] - 4*	*Day 5*	*Day 6 - 11*	*Day 12*	*15 (± 2) days following last soticlestat dose*
	----------*Confinement [b]*----------							*Contact*

[a] Day 1 of Period 2 will also be considered Day 5 of Period 1.
[b] Participants will start the confinement on Day -1 of Period 1 and remain confined until Day 12 of Period 2.
[c] Study Exit is defined as the end of last treatment period.
Abbreviations: C-I = Check-in, FU = Follow-up, PK = Pharmacokinetic, S = Screening.

Table 2.b Dose Regimens for Study Drugs in Part 1

Study Drug	*Dose*	*Dose Regimen*	*Number of Days on Study Drug*
Soticlestat CCI	*300 mg* CCI	*Single dose, oral*	*Day 1 Period 1 and Day 5 Period 2*
Itraconazole (oral solution)	*200 mg (10 mL of 20 mg/mL oral solution)*	*QD, oral*	*Days 1 through 11 Period 2*

Abbreviations: QD = Once daily

Table 2.c Study Design for Part 2

S	*Period 1*			*Period 2*				*FU*
	C-I and Predose Assessments	*Soticlestat Dosing, PK Sampling, and Study Assessments*	*PK Sampling and Study Assessments*	*Mefenamic Acid Dosing and Study Assessments*	*Co-administration (Mefenamic Acid and Soticlestat), PK Sampling, and Study Assessments*	*Mefenamic Acid Dosing, PK Sampling, and Study Assessments*	*Study Exit [c] (PK Sampling and Study Assessments)*	
Within 28 days prior to first dosng	*Day -1*	*Day 1*	*Day 2 – 5 [a]*	*Day 1 [a]*	*Day 2*	*Day 3 - 7*	*Day 8*	*15 (± 2) days following last soticlestat dose*
	----------*Confinement [b]*----------							*Contact*

[a] Day 1 of Period 2 will also be considered Day 5 of Period 1
[b] Participants will start the confinement on Day -1 of Period 1 and remain confined until Day 8 of Period 2.
[c] Study Exit is defined as the end of last treatment period.
Abbreviations: C-I = Check-in, FU = Follow-up, PK = Pharmacokinetic, S = Screening.

Table 2.d Dose Regimens for Study Drugs in Part 2

Study Drug	*Dose*	*Dose Regimen*	*Number of Days on Study Drug*
Soticlestat CCI	*300 mg* CCI	*Single dose, oral*	*Day 1 Period 1 and Day 2 Period 2*
Mefenamic acid (capsules)	*500 mg (2 x 250 mg capsules)*	*Once, oral*	*Initial dose - Morning of Day 1 of Period 2*
	250 mg (1 x 250 mg capsule)	*Q6H, oral*	*All subsequent doses following the morning dose on Day 1 of Period 2 – Days 1 through 7 of Period 2*

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

Part 1: DDI with itraconazole

Participants will be screened within 4 weeks (28 days) prior to the first dosing (Day -28 to first dosing on Day 1 of Period 1). Upon completion of screening, qualified participants will be admitted to the study site on Day -1 of Period 1 and will remain confined until completion of study procedures on Day 12 of Period 2.

In Period 1, on Day 1, participants will receive a single oral dose of 300 mg soticlestat CCI *. Blood samples for the PK of soticlestat* CCI *will be collected at scheduled time points from predose through 96 hours postdose. There will be a washout period of exactly 4 days between soticlestat dose in Period 1 and the first itraconazole dose in Period 2.*

In Period 2, from Days 1 to 11, participants will receive a once-daily (QD) oral dose of 200 mg itraconazole. On the morning of Day 5, participants will receive a single oral dose of 300 mg soticlestat CCI *co-administered with the oral dose of 200 mg itraconazole. Blood samples for the PK of soticlestat* CCI *will be collected at scheduled time points from predose on Day 5 through 168 hours postdose.*

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

After discharge, the clinical research unit (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 adverse events (AEs) have occurred and/or any concomitant medications were taken since the last study visit. If clinically significant findings are observed upon discharge, participants may return to the CRU for re-evaluation per Investigator's discretion.

Part 2: DDI with mefenamic acid

Participants will be screened within 4 weeks (28 days) prior to the first dosing (Day -28 to first dosing on Day 1 of Period 1). Upon completion of screening, qualified participants will be admitted to the study site on Day -1 of Period 1 and will remain confined until completion of study procedures on Day 8 of Period 2.

In Period 1, on Day 1, participants will receive a single oral dose of 300 mg soticlestat CCI *Blood samples for the PK of soticlestat* CCI *will be collected at scheduled time points from predose through 96 hours postdose. There will be a washout period of exactly 4 days between soticlestat dose in Period 1 and the first mefenamic acid dose in Period 2.*

In Period 2, participants will receive mefenamic acid every 6 hours (Q6H) from Days 1 to 7. The initial oral dose on the morning of Day 1 will be 500 mg and all subsequent oral doses will be 250 mg. On the morning of Day 2, participants will receive a single oral dose of 300 mg soticlestat CCI *co-administered with the morning dose of 250 mg mefenamic acid. Blood samples for the PK of soticlesta* CCI *will be collected at scheduled time points from predose on Day 2 through 1*

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

After discharge, the CRU will contact all participants (including participants who terminate the study early) 15 (±2) 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.

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

CCI

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[redacted]

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 analysis set.

5.2 Safety Set

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

- Insufficient data to determine a reliable CCI value and other CCI dependent parameters
- 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
- 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
- Concentration data file used for PK analysis
- PK parameter WinNonlin® output file used to generate the TFLs
- Linear mixed-effect 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 clinical study report.

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, 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 Dictionary, and SAS version used for creating the datasets. Study drug refers to soticlestat or itraconazole in Part 1 or soticlestat or mefenamic acid in Part 2.

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 and listed by participant.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized by study part 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 24.1. 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 01Sep2021_b3 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, 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. All clinical safety data will be listed by study part, participant, and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically. Subjects 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 drugs (related or not related), relationship to COVID-19 or COVID-19 vaccine, frequency, and action relative to the study drugs 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 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 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
Part 1	
Period 1 Day 1 soticlestat dosing ≤ Date and Time of AE < Period 2 Day 1 itraconazole dosing	Soticlestat Alone
Period 2 Day 1 itraconazole dosing ≤ Date and Time of AE < Period 2 Day 5 soticlestat dosing	Itraconazole Alone
Period 2 Day 5 soticlestat dosing ≤ Date and Time of AE < end of follow-up	Soticlestat + Itraconazole
Part 2	
Period 1 Day 1 soticlestat dosing ≤ Date and Time of AE < Period 2 Day 1 mefenamic acid dosing	Soticlestat Alone
Period 2 Day 1 mefenamic acid dosing ≤ Date and Time of AE < Period 2 Day 2 soticlestat dosing	Mefenamic Acid Alone
Period 2 Day 2 soticlestat dosing ≤ Date and Time of AE < end of follow-up	Soticlestat + Mefenamic Acid

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 participant (or >1 participant) in either treatment, 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 drugs. 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 each relationship to each study drug, 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 study report.

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:

Part 1: screening, Period 1 Day -1, Period 1 Day 3, Period 2 Day 4 predose, Period 2 Day 7 predose, and Period 2 Day 12 (or at early termination if applicable)

Part 2: screening, Period 1 Day -1, Period 1 Day 3, Period 2 Day 1 predose, Period 2 Day 4 predose, and Period 2 Day 8 (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 at each scheduled visit for each study part. 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 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:

Part 1: screening, Period 1 Day 1 predose, Period 1 Day 1 Hours 0.5 and 1.5, Period 1 Day 2, Period 2 Day 4 predose, Period 2 Day 5 Hours 0.5 and 1.5, Period 2 Day 6 predose, and Period 2 Day 12 (or at early termination if applicable)

Part 2: screening, Period 1 Day 1 predose, Period 1 Day 1 Hours 0.5 and 1.5, Period 1 Day 2, Period 2 Day 1 predose, Period 2 Day 2 Hours 0.5 and 1.5, Period 2 Day 3 predose, and Period 2 Day 8 (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 for each study part. 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 study part and participant.

6.7.5 12-Lead Electrocardiogram

Single 12-lead ECGs will be collected at the following time points:

Part 1: screening, Period 1 Day 1 predose, Period 2 Day 4 predose, and Period 2 Day 12 (or at early termination if applicable)

Part 2: screening, Period 1 Day 1 predose, Period 2 Day 1 predose, and Period 2 Day 8 (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 for each study part. Baseline is defined as the last assessment including rechecks taken prior to the first dose in the study. Post-baseline 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, 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, > 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

In both study parts, 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 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 of each study part and Period 2 Day 12 (or at early termination, if applicable) in Part 1 and Period 2 Day 8 (or at early termination, if applicable) in Part 2, 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 study part and 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 itraconazole and mefenamic acid will be listed by study part and participant.

6.8 Pharmacokinetic Analysis

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

Table 6.b Collection of Blood Samples for Pharmacokinetic Analysis

Analytes	Matrix	Study Part	Period	Scheduled Time (Hours)*
Soticlestat CCI [redacted]	Plasma	1	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 postdose.
		1	2	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, 144, and 168 hours postdose.
		2	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 postdose.
		2	2	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.

*The actual date and time of sample collection will be recorded on the source document in the CRF.

Concentrations of plasma soticlestat, CCI [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, CCI [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}, and AUC_{∞} data will be analyzed using a linear mixed-effects model, separately. The model will include treatment (soticlestat with and without itraconazole/mefenamic acid) as a fixed effect and participant as a random effect. The point estimates and the 90% CIs for the GMRs of AUC_{last}, AUC_{∞}, and C_{max} for soticlestat with versus without itraconazole/mefenamic acid 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 AUC_{last}, AUC_{∞}, and C_{max}.

The following treatment contrast will be evaluated separately: soticlestat + itraconazole relative to soticlestat alone and soticlestat + mefenamic acid relative to soticlestat alone.

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 PARTICIPANT;
MODEL LN_PARAM = TREAT / DDFM=KR;
RANDOM PARTICIPANT;
ESTIMATE "Soticlestat + Itraconazole vs Soticlestat Alone" TREAT -1 1 / CL ALPHA=0.1 E;
LSMEANS TREAT;
RUN;
```

Programming note: For Part 2, "Mefenamic Acid" will replace "Itraconazole."

CCI

[redacted]

The 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 comparisons of interest are the same as for the linear mixed-effects analysis above.

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

CCI [redacted]

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')
PPD	Biostatistics Approval	19-Oct-2021 23:32 UTC