Statistical Analysis Plan

NCT Number: NCT05602818

Title: A Phase 1, Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, 5-Way Crossover Study Evaluating the Abuse Potential of Soticlestat (TAK-935) in Healthy Adult Nondependent Recreational Drug Users With Central Nervous System Depressant Experience

Study Number: TAK-935-1012

Document Version and Date: Amendment 2.0, 10 August 2023

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

STATISTICAL ANALYSIS PLAN

Study Number: TAK-935-1012

Study Title: A Phase 1, Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, 5-Way Crossover Study Evaluating the Abuse Potential of Soticlestat (TAK-935) in Healthy Adult Nondependent Recreational Drug Users With Central Nervous System Depressant Experience

Phase: 1

Version: Amendment 2

Date: 10-AUG-2023

Prepared by:

[redacted], Statistics

[redacted], Statistics

Based on:

Protocol Version: Amendment 1

Protocol Date: 15 March 2023

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	21-OCT-2022	Not Applicable
Amendment 1	20-JUL-2023	Address the changes outlined in Protocol Amendment 1
Amendment 2	10-AUG-2023	Clarify methodology and add supplementary analyses

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
[redacted]	[redacted]
BLQ	below the limit of quantitation
CI	confidence interval
C_{max}	maximum observed concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
E_{max}	maximum effect
[redacted]	[redacted]
H_0	null hypothesis
H_a	alternative hypothesis
ICF	informed consent form
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
PD	pharmacodynamic
[redacted]	[redacted]
PT	Preferred Term (MedDRA)
Q1	25th percentile
Q3	75th percentile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	System Organ Class
$t_{1/2}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
t_{max}	time of first occurrence of C_{max}
VAS	visual analogue scale
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To evaluate the relative abuse potential of soticlestat compared with placebo and alprazolam under fasted conditions in healthy adult nondependent recreational drug users with CNS (central nervous system) *depressant experience.*

1.1.2 Secondary Objectives

To evaluate additional PD (pharmacodynamic) *effects and safety of soticlestat compared with placebo and alprazolam under fasted conditions in healthy adult nondependent recreational drug users with CNS depressant experience.*

1.1.3 [redacted]

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint

Maximum effect (E_{max}) for Drug Liking ("at this moment") as assessed by a bipolar visual analogue scale (VAS) (0-100 points).

1.2.2 Secondary Endpoints, PD

1.2.2.1 Key Secondary Endpoints

- *Overall Drug Liking (E_{max}) assessed by a bipolar VAS (0-100 points).*
- *Take Drug Again (E_{max}) assessed "overall" by a bipolar VAS (0-100 points).*

1.2.2.2 Other Secondary Endpoints

- *Bad Drug Effects (E_{max}) assessed "at this moment" by a unipolar VAS (0-100 points).*
- *Good Drug Effects (E_{max}) assessed "at this moment" by a unipolar VAS (0-100 points).*
- *High (E_{max}) assessed "at this moment" by a unipolar VAS (0-100 points).*

1.2.3 Secondary Endpoint, Safety

Incidence of TEAEs (treatment-emergent adverse events).

1.2.4 Other Safety Endpoints

- *Clinical laboratory values, vital signs, and electrocardiograms (ECGs).*
- *Columbia-Suicide Severity Rating Scale (C-SSRS).*

1.2.5 [redacted]

[redacted]

1.2.6 [redacted]

[redacted]

1.3 Estimand

Not applicable.

2.0 STUDY DESIGN

This is a phase 1, randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover study to determine the relative abuse potential of single oral doses of soticlestat compared to a single oral dose of 2 mg of alprazolam and placebo in healthy adult, nondependent recreational drug users with CNS depressant experience.

This study will consist of 4 phases: Screening, qualification, treatment, and follow-up.

Each participant will participate in a screening visit (Visit 1) to determine eligibility within 28 days of the first dose in the qualification phase. Eligible participants will participate in an

inpatient, qualification phase (from Day -1 through Day 3) to determine if participants are able to discriminate the drug effects of the positive control, 2 mg of alprazolam, when compared to placebo, and to demonstrate that they are able to tolerate the administered alprazolam 2 mg dose.

Each participant will be randomized to receive alprazolam or placebo in a double-blind, crossover manner. On each dosing day during the qualification phase, participants will fast for at least 8 hours predose and for 4 hours postdose. Drug administration on the 2 qualification phase days will be separated by an approximately 24-hour washout period. Selected PD and safety assessments will be performed prior to and after each study drug administration.

Eligible participants who qualify in the qualification phase (criteria described in Section 7.3 of the study protocol*) may be released from the study site and if continue to meet eligibility criteria will enter the inpatient treatment phase. The last study drug administration in the qualification phase and the first study drug administration in the treatment phase will be separated by a washout interval of at least 4 days. If participants are released after the qualification phase, they will enter into the clinical research unit (CRU) the day before dosing (baseline [Bs]/treatment Day -1) of the treatment period.*

If participants are confined to the clinic from qualification phase to treatment phase, they need not perform the Bs/treatment Day -1 assessments. Site should ensure participant meets qualification eligibility criteria prior to randomizing these participants and continue to monitor for SAEs (serious adverse events) *and document concomitant medications.*

During the treatment phase of the study, participants will receive medication (double-dummy) on each dosing day and they should remain confined throughout the treatment phase. If participants are confined to the clinic throughout the treatment phase, they need not repeat the Bs/treatment Day -1 procedures prior to each treatment period. Treatment periods will be separated by a minimum of 7 days between dosing.

Each participant will be randomized to receive oral treatments (1 in each treatment phase period) in a double-blind, crossover fashion as shown in Figure 2.a (Table 6.a of study protocol).

The treatment phase will include 5 treatment periods as described in Figure 2.a (Table 6.a of study protocol).

Study drug administration during each treatment phase period will occur on the first day (a single dose) of each treatment period followed by PD, [redacted] *and safety assessments for up to 24 hours postdose at the study site. At each treatment phase period, participants will fast for at least 8 hours predose and for 4 hours postdose. Although soticlestat has a relatively short plasma $t_{1/2}$ (2.6 to 8.7 hours for oral tablets), study drug administrations during the treatment phase periods will be separated by a washout interval of 7 days because the PD biomarker for soticlestat treatment (ie, 24HC reduction in plasma) returns to baseline slowly but within 7 days after treatment is stopped (ie, PD washout).*

All participants, including those who discontinue early (except those who withdraw consent and refuse further contact), will complete the safety follow-up visit 1 week (± 3 days) after the last administered blinded study drug in the treatment phase.

An overview of the study design described above is provided in Figure 2.a (Table 6.a of study protocol). [redacted]

Figure 2.a Schematic of Study Design (Table 6.a from Study Protocol)

Screening Phase	Randomization to Sequence Q1 and Q2	Sequence	Qualification Phase		Randomization to Sequence 1 -10	Sequence [b]	Treatment Phase[a]					Follow-up Phase
			Day 1	Day 2			Period 1	Period 2	Period 3	Period 4	Period 5	Discharge
			Treatment				Treatment					
within 28 days of Qualification Phase		Q1	Alprazolam	Placebo		1	A	B	E	C	D	~ 7±3 days after final dose given at the last treatment period
		Q2	Placebo	Alprazolam		2	B	C	A	D	E	
						3	C	D	B	E	A	
						4	D	E	C	A	B	
						5	E	A	D	B	C	
						6	D	C	E	B	A	
						7	E	D	A	C	B	
						8	A	E	B	D	C	
						9	B	A	C	E	D	
						10	C	B	D	A	E	

[a] Treatment description – treatment phase

Treatment A: Soticlestat 300 mg
Treatment B: Soticlestat 600 mg
Treatment C: Soticlestat 900 mg
Treatment D: Alprazolam 2 mg
Treatment E: Placebo

[b] Sequences are based on a Williams design (Williams 1949) (ie, uniform within sequences, unform within periods, and balanced with respect to first-order carryover effects). The specific sequences used here were calculated using the crossdes package (Package 'crossdes', Construction of crossover designs, April, 2022) in R (R Core Team [2021]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria)

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

The following hypotheses will be tested for the primary PD endpoint of Drug Liking "at this moment" VAS E_{max}.

1. *Validation test of the sensitivity and integrity of the study: Does the positive control (C) produce mean responses that show greater abuse potential compared to placebo (P)?*

$$H_0: \mu_C - \mu_P \leqslant 15 \text{ vs. } H_a: \mu_C - \mu_P > 15$$

where μ_C and μ_P are the mean Drug Liking VAS E_{max} for alprazolam and placebo, respectively. The margin of 15 was selected based on previous studies of this type (CDER [Center for Drug Evaluation and Research]*, 2022. Application Number: 215904, Statistical Reviews).*

2. *Does the test drug (T) produce mean responses that show less abuse potential compared to positive control?*

   $$H_0: \mu_C - \mu_T \leqslant 0 \text{ vs } H_a: \mu_C - \mu_T > 0$$

   where μ_T is mean Drug Liking VAS E_{max} for soticlestat. This hypothesis will be tested separately for each soticlestat dose. Rejection of each null hypothesis would suggest lower relative abuse potential of soticlestat compared to alprazolam.

3. *Does the test drug produce mean responses that show similar abuse potential compared to placebo?*

   $$H_0: \mu_T - \mu_P \geqslant 11 \text{ vs } H_a: \mu_T - \mu_P < 11$$

   This hypothesis will be tested separately for each soticlestat dose. Rejection of each null hypothesis would suggest that soticlestat does not produce an abuse-related signal. The margin of 11 was selected based on Chen and Bonson (Chen and Bonson 2013)

All hypotheses for the primary endpoint will be tested at 1-sided 0.05 level of significance. The hypotheses will be tested sequentially in the order listed. Within the second and third hypotheses, testing will be ordered from low dose to high dose.

In the sequential testing procedure, a non-statistically significant test will result in cessation of testing the subsequent hypotheses.

3.2 Multiplicity Adjustment

Hypotheses are tested sequentially and testing subsequent hypotheses will cease when a test is not statistically significant. *All hypotheses will be evaluated using nominal p-values.*

4.0 SAMPLE-SIZE DETERMINATION

The qualification phase of the study is based on a 2x2 crossover design with oral doses of alprazolam 2 mg and matching placebo. The treatment phase is based on a 5-treatment, 10-sequence, 5-period Williams square crossover design with treatments A, B, C, D, and E as defined previously.

Approximately 140 participants will be enrolled into the qualification phase of the study, randomized equally to the 2 sequences. Approximately 65 qualified participants will be randomized equally to the 10 sequences in the treatment phase, with the intent to ensure that at least 39 participants are in the modified completer analysis set.

Participants who are randomized but who are prematurely discontinued or eliminated from the modified completer analysis set may be replaced to ensure that the size of the modified completer analysis set is sufficient, sequences are approximately balanced, and there is at least 1 participant per sequence. Replacement participants will be assigned to the same treatment sequence as the original participant.

It is estimated that, in the treatment phase, a sample size of 39 participants in the modified completer analysis set will provide at least 90% power to test each of the hypotheses for the primary PD endpoint.

Power calculations used a paired t-test and assumed a true standard deviation (SD) of 23 points for within-participant differences for each planned treatment comparison on the Drug Liking VAS E_{max}, a true mean difference of 26 points between alprazolam 2 mg and placebo, and a true mean difference of 0 points between placebo and each dose of soticlestat.

The assumptions on the mean and standard deviation of the difference between alprazolam and placebo were derived from published data. (Chen and Bonson 2013, Levy-Cooperman, et al. 2016, Schoedel, Stockis and Sellers 2018)

The derivation of SD for within-participant differences was based on SD of 16 for alprazolam 2 mg and 17 for placebo, and correlation of 0. The resulting SD of 23 for the difference was then used in power calculations for all other hypotheses.

Alternatively, because soticlestat is believed to have similar abuse potential to placebo, if soticlestat and placebo are assumed to have the same SD of 17 and correlation 0.7, then the SD of within-participant differences would be approximately 13. With this assumed SD, the power with a sample size of 39 participants in the modified completer analysis set is at least 95% for testing the hypothesis comparing each dose of soticlestat to placebo if the assumed mean difference between them is at most 4 points. Correspondingly, if the mean difference between each dose of soticlestat and alprazolam 2 mg is at least 22 (=26-4) points, and correlation is 0 (hence SD is 23 for within-participant differences), the power is at least 99% to test the hypothesis comparing each dose of soticlestat to alprazolam 2 mg.

5.0 ANALYSIS SETS

5.1 Qualification Phase

5.1.1 Qualification Randomized Analysis Set

All participants who are randomized in the qualification phase.

5.1.2 Qualification Safety Analysis Set

All participants who receive at least 1 dose of study drug (ie, placebo or alprazolam) in the qualification phase. All safety evaluations in the qualification phase will be performed using this analysis set.

5.2 Treatment Phase

5.2.1 Randomized Analysis Set

All participants who are randomized in the treatment phase.

5.2.2 Safety Analysis Set

All participants who receive at least 1 dose of study drug in the treatment phase. All safety evaluations in the treatment phase will be performed using this analysis set.

5.2.3 Completer Analysis Set

All participants in the randomized analysis set who complete all treatment periods of the treatment phase and have at least 1 response on the VAS for Drug Liking "at this moment" within 2 hours postdose (hence within approximately 2 hours of historical time of first occurrence of $C_{max}[t_{max}]$ of soticlestat and alprazolam) for each treatment. This analysis set may be used for supportive PD analyses.

5.2.4 Modified Completer Analysis Set

All participants in the completer analysis set, excluding those whose Drug Liking "at this moment" VAS E_{max} scores meet the following elimination criteria:

a) Similar E_{max} scores (within a 5-points difference) for a participant across all study treatments (including placebo); i.e., Max(all E_{max} scores) – Min(all E_{max} scores) ≤ 5.

OR

b) E_{max}(positive control) ≤ 55

OR

c) Emax(placebo) – Emax(positive control) ≥5

This analysis set will be used for PD analyses.

5.2.5 [redacted]

[redacted]

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Variables will be summarized descriptively where applicable. For categorical variables, the count (n) and percent (%) will be displayed. Unless otherwise stated, the denominator for percentages is the number of participants in the analysis set within each group. Generally, "Missing" will be displayed as a category to represent missing data, where applicable. If missing is not a category, then the denominator is the number of participants with non-missing values. For continuous variables, summary tables will include the number of participants with non-missing values, mean, median, SD, minimum, and maximum values.

Unless indicated otherwise, when descriptive summaries are reported, they will be presented separately by study phase and grouped as follows: PD endpoints will be presented by treatment;

[redacted] safety endpoints will be presented by treatment and overall; demographics will be presented overall. All log transformations will be based on natural logarithms.

Counts will be presented as integers. Percentages will be presented to one decimal. For continuous variables, 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 will be the predose value within a treatment period where available. Otherwise, baseline will be last observation prior to taking any study drug (placebo, alprazolam, or soticlestat).

All p-values will be rounded to 4 decimal places prior to assessment of statistical significance, and will be reported to 4 decimal places, with p-values that would round to 0.0000 presented as <0.0001.

6.1.1 Handling of Treatment Misallocations

Unless otherwise stated, participants who are misallocated treatments will be analyzed per the treatment they received rather than per the treatment regimen to which they were randomized.

6.2 Study Information

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

6.3 Disposition of Participants

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

A listing of participants not meeting the qualification criteria together with reason for failure to pass the qualification phase will be provided.

All protocol deviations will be listed and significant protocol deviations will be flagged.

A summary table for all analysis sets will be created. A listing indicating whether each participant was included or excluded from each analysis set will be provided.

The qualification randomized analysis set and the randomized analysis set will be used for presenting the above tables and listings for the qualification phase and treatment phase, respectively.

Participants who failed screening will be listed with primary reasons for screen failure.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic data will be summarized using the qualification safety analysis set and the safety analysis set. Results for each analysis set will be presented overall. Variables to be presented include age, sex, ethnicity, race, height, weight, and body mass index. Demographic data will also be listed as recorded on the CRF, including the date of informed consent and protocol version. The listing will be based on the qualification safety analysis set and will include an identifier indicating whether the participant was dosed in the treatment phase.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the participant has any significant conditions that resolved at or before signing informed consent.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of the ICF. These include clinically significant laboratory, ECG, or physical examination abnormalities noted at Visit 1, according to the judgment of the investigator. The condition (ie, diagnosis) should be described and recorded in the eCRF.

Each participant's medical history and concurrent medical conditions will be listed using the qualification safety analysis set with a flag indicating whether the participant was dosed in the treatment phase. 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

Any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 6 months before signing of informed consent will be obtained.

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the participant over the counter. Concomitant medication is not provided by the sponsor. At each study visit, participants will be asked whether they have taken any medication other than the study drug (used from signing of informed (e)consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

All medication history and concomitant medications recorded during the study will be coded using the World Health Organization (WHO) Drug Dictionary and listed by participant. 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. Medications stopped before the administration of study drug will be identified as "prior" in the listing.

6.6 Substance Use History

A history of all drugs used for recreational/non-medicinal purposes (ie, psychoactive effects) in the past 2 years will be collected. History, including drug preference (ie, drug of choice) and frequency of use (ie, average number of uses per week before screening) and date/time of last use, will be collected using reported drug names, by drug class (eg, cannabinoids, depressants, dissociative anesthetics, hallucinogens, opioids and morphine derivatives, stimulants).

A history of alcohol use (ie, average number of drinks [beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz]] per week and number of occasions of binge drinking [more than 3 drinks/5 drinks in a sitting for female/male participants]) in the 6 months before screening and smoking (smoker/non-smoker, if smoker, number of cigarettes per day) will also be collected.

Information on recreational drug use, alcohol use, and smoking obtained as part of substance use history will be summarized based on the safety analysis set.

Each participant's drug use history for recreational/non-medicinal purposes will also be listed as recorded on the CRF including the drug name and class, drug of choice, route of administration, number of times used in the past 12 weeks and number of times used in the past two years. The listing will be done using the safety analysis set.

6.7 PD Analysis

6.7.1 PD Endpoints

PD measures will be administered electronically. This section describes the measures and the study endpoints derived from them.

6.7.1.1 Subjective Effects

Subjective drug effects are assessed using standardized questionnaires, each administered as a 100-point VAS at multiple postdose timepoints. For some questionnaires a predose assessment is also done. *The VAS may be administered as bipolar or unipolar scales, as appropriate, and the choice is determined by the nature of the subjective effect being measured. When VAS are administered as bipolar scales, the neutral point equals 50 (Drug Liking, Overall Drug Liking, Take Drug Again, Alertness/Drowsiness VAS). The neutral point will also be labeled with an anchor, such as "neither like nor dislike." When VAS are administered as unipolar scales, the neutral point equals 0, and anchors will be presented using text such as "Not at all" (score = 0) to "Extremely" (score = 100; eg, Good, Bad, High, and Any Effects VASs). Scales that refer specifically to drug (eg, Drug Liking, Good Effects VAS, Bad Effects VAS, and Any Effects VAS) are not administered predose.*

For each questionnaire, several derived quantities may be used as endpoints for analysis, as follows:

- Maximum effect (E_{max}) is the maximum value of the VAS scores across all timepoints at which the questionnaire is administered after each treatment (up to 24 hours postdose).

[redacted]

Table 6.a shows each VAS and its associated endpoints to be used in this study, along with classification of each endpoint as primary, key secondary, other secondary, [redacted]

Table 6.a VAS Endpoint Descriptions

Instrument	Question Text	Response Anchors	Type of Scale	Interpretation	Assessment Timepoints During Treatment Phase	Derived Value for Analysis	Endpoint Classification
Drug liking	At this moment, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking	Bipolar	Balance	[redacted]	E_{max}	Primary
Overall drug liking	Overall, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking	Bipolar	Balance		E_{max}	Key Secondary
Take drug	I would	0: Definitely	Bipolar	Balance		E_{max}	Key Secondary

Table 6.a VAS Endpoint Descriptions

Instrument	Question Text	Response Anchors	Type of Scale	Interpretation	Assessment Timepoints During Treatment Phase	Derived Value for Analysis	Endpoint Classification
again	take this drug again	not 50: Neutral 100: Definitely so			[redacted]	[redacted]	[redacted]
Bad effects	At this moment, I feel bad drug effects	0: Not at all 100: Extremely	Unipolar	Negative	[redacted]	E_{max}	Other Secondary
Good effects	At this moment, I feel good drug effects	0: Not at all 100: Extremely	Unipolar	Positive	[redacted]	E_{max}	Other Secondary
High	At this moment, I am feeling high	0: Not at all 100: Extremely	Unipolar	Positive	[redacted]	E_{max}	Other Secondary
[redacted]							

6.7.1.2 [redacted]

[redacted]

[redacted]

6.7.2 PD Analysis: General Considerations

PD endpoints will only be analyzed or summarized for the treatment phase unless otherwise stated. PD data will be listed for both phases using the randomized analysis set or qualification randomized analysis set, as appropriate.

For each PD endpoint, the number of participants with non-missing values, mean, standard error, minimum, first quartile (Q1), median, third quartile (Q3) and maximum for each treatment and each paired difference among treatments will be reported for the treatment phase.

The mean response for each treatment over time will be plotted for the primary and secondary PD endpoints.

Summaries of PD endpoints will use the modified completer analysis set.

The primary and key secondary endpoints will be summarized for the qualification phase by treatment and paired difference for the modified completer analysis set using standard descriptive statistics. The data will be evaluated to confirm that an appropriate population was selected for the treatment phase.

6.7.3 PD Analysis: Primary Endpoint

6.7.3.1 Derivation of Endpoint

The primary endpoint is the E_{max} for Drug Liking "at this moment" VAS. Refer to Section 6.7.1.1 for the derivation.

6.7.3.2 Main Analytical Approach

Analysis of the primary endpoint will be performed on the modified completer analysis set. A linear mixed effects model containing treatment, period, sequence, and first-order carryover (if applicable) as fixed effects, and participant as random effect, is planned to be used to evaluate the hypotheses for the primary endpoint. The Kenward-Roger method for calculating denominator degrees of freedom will be used. Refer to Section 3.1 for statements of the statistical hypotheses.

Prior to applying the model, homogeneity of variances across treatments will be tested using a restricted likelihood ratio test. This test will be implemented using the SAS procedure GLIMMIX with COVTEST statement. If the test is statistically significant at the 0.05 level,

variances will be considered heterogeneous. Otherwise, variances will be considered homogeneous.

If the variances are homogeneous, the model will constrain variances to be equal across treatment groups. This is implemented using the SAS procedure MIXED with the option "RANDOM SUBJECT" included. If variances are heterogeneous, the model will allow unequal variances across treatment groups. This will be implemented by adding the option "REPEATED/SUBJECT=SUBJECT GROUP=TREATMENT" to the "RANDOM SUBJECT" option.

After determining whether the treatment variance is homogeneous or heterogeneous, the residuals from the model will be investigated for normality using the Shapiro-Wilk W-test. If the test has p-value <0.05, the residuals will be considered not normally distributed. Otherwise, the residuals will be considered normally distributed.

If the residuals are normally distributed, it will be determined whether the carryover effects should be included in the model. Carryover effects are defined as the effect of the treatment administered in the previous treatment period. As there are no carryover effects in treatment period 1, placebo will be used in this period. If the carryover effect has p-value <0.25, the term will be included in the model. Otherwise, the term will be dropped.

If the residuals are not normally distributed, the distribution of the paired difference for each contrast will be examined in terms of normality and skewness. Each paired difference will be investigated for normality using the Shapiro-Wilk W-test. If the test has p-value ⩾0.05, the paired difference will be considered normally distributed, and a paired t-test will be used for analysis. If the paired difference is not normally distributed, that is, the W-test has p-value <0.05, the following criteria on skewness will be used to determine whether the paired t-test or sign test is used for testing:

a) If the alternative hypothesis is upper-tailed, and skewness is [0, 0.5], the paired t-test will be used.

b) If the alternative hypothesis is upper-tailed, and skewness <0 or skewness >0.5, the sign test will be used.

c) If the alternative hypothesis is lower-tailed, and skewness is [-0.5, 0], the paired t-test will be used.

d) If the alternative hypothesis is lower-tailed, and skewness <-0.5 or skewness >0, the sign test will be used.

e) If the alternative hypothesis is two-tailed, and skewness is [-0.5, 0.5], the paired t-test will be used.

f) If the alternative hypothesis is two-tailed, and skewness <-0.5 or skewness >0.5, the sign test will be used.

If the sign test is used for analysis, the median of the paired difference, first quartile (Q1), third quartile (Q3), 1-sided 95% CI, and p-value from the sign test will be displayed (Hollander and

Wolfe 1999). Note that the calculation of the p-value of the sign test excludes paired differences in scores that are equal to zero after subtracting the margin from the differences. The calculation of CI does not exclude any paired difference (Hollander and Wolfe 1999). The conclusions will be based on p-values.

If the paired t-test is used for analysis, the mean difference, SE, 1-sided 95% CI, and p-value from the t-test will be displayed.

If a mixed effects model is used for analysis, the least squares mean difference, SE, 1-sided 95%, and p-value from the contrast test will be displayed.

6.7.3.3 Supplementary Analyses

Regardless of the main analytic approach taken per section 6.7.3.2, results of the mixed model (including/excluding carryover effects) and paired t-test will be displayed as a supplementary analysis.

If the modified completer analysis set differs from the completer analysis set by more than 5 participants, a supplementary analysis will be conducted using the Completer Analysis Set and following the main analytic approach described in Section 6.7.3.2.

If a mixed effects model is used for the main analysis and the carryover effect has p-value <0.05, a supplementary first-period analysis will be conducted using an ANOVA model containing treatment group as the fixed effect. The difference in least squares means, 1-sided 95% CIs of the difference, and p-values will be provided for each treatment comparison.

6.7.4 PD Analysis: Secondary Endpoints

6.7.4.1 Secondary Endpoints Analysis

The key secondary endpoints are E_{max} of Overall Drug Liking and E_{max} of Take Drug Again. The other secondary endpoints are E_{max} of Bad Drug Effects, E_{max} of Good Drug Effects, and E_{max} of High. Refer to Section 6.7.1.1 for derivations and descriptions of these endpoints.

The following hypotheses will be evaluated for key and other secondary endpoints. Comparisons among treatments will be evaluated at 1-sided significance level 0.05 for hypotheses 1 and 2, and 2-sided significance level 0.10 for hypothesis 3 as stated below.

1. *Positive control (alprazolam) (C) vs placebo (P):*

$$H_0: \mu_C - \mu_P \leq 0 \text{ vs } H_a: \mu_C - \mu_P > 0$$

2. *Positive control (alprazolam) (C) vs each dose of soticlestat (T):*

$$H_0: \mu_C - \mu_T \leq 0 \text{ vs } H_a: \mu_C - \mu_T > 0$$

3. *Each dose of soticlestat (T) vs placebo (P):*

$$H_0: \mu_T - \mu_P = 0 \text{ vs } H_a: \mu_T - \mu_P \neq 0$$

No adjustments to p-values will be made. All hypotheses will be evaluated using nominal p-values.

6.7.4.2 Main Analytical Approach

Key and other secondary PD endpoints will be analyzed with the same linear mixed effects model or nonparametric approaches (as appropriate) as the primary endpoint analysis, using the modified completer analysis set and following the same strategy for determining the analysis method. If a PD endpoint is based on a VAS that has a baseline (predose) measurement, the mixed effects model for that endpoint will always include baseline as a covariate. The statistical hypotheses to be evaluated are described in Section 6.7.4.1. For hypothesis 3, the CIs presented will be 2-sided at the 90% level, and p-values will be 2-sided.

6.7.4.3 Sensitivity and Supplementary Analysis

For key secondary endpoints, regardless of the main analytic approach taken per section 6.7.4.2, results of the mixed model (including/excluding carryover effects) and the paired t-test will be displayed as a supplementary analysis.

6.7.5 [redacted]

[redacted]

6.8 Safety Analysis

Safety analyses for the qualification phase will be based on the qualification safety analysis set. Safety analyses for the treatment phase will be based on the safety analysis set.

6.8.1 Adverse Events

All AEs captured in the database will be listed by participant and will include reported term, coded terms (SOC and PT), severity (mild, moderate, severe), relationship to study drug (related or not related), pattern (once, intermittent, continuous), and action relative to the study drug as recorded in the CRF. All AEs occurring during this study will be coded using MedDRA version 24.0 or later.

Only TEAEs will be summarized. A TEAE is defined as an AE that starts or worsens during or after the first dose of study drug in each study phase. Each TEAE will be attributed to the treatment prior to and the closest to the AE based on the AE onset date and time. If the onset time of an AE is missing and the onset date is the same as a treatment dosing date, then the AE will be counted under the treatment given on the same day. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment emergent for the most recent prior 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 in summary tables, and if relationship is missing, the AE will be counted as related in summary tables. Any medical condition starting or worsening after the ICF but before the first dose of study drug in the qualification phase will be classified as pre-treatment event.

Summary of TEAEs will be presented separately for each study phase. Summary tables will include number and percent of participants reporting the TEAE and number of events by treatment and overall. The denominators for percent calculations will be the number of participants dosed for each treatment.

Summary tables will also be generated for: SAEs, SAEs related to study drug, TEAEs leading to study drug discontinuation, TEAEs related to study drug, the most commonly reported non-serious TEAEs (ie, those events reported by >2 participants excluding SAEs), TEAEs by severity, and TEAEs by relationship to study drug. If a participant has multiple TEAEs with different severity levels within the same PT, the participant will be counted in the most severe category only. If a participant has both related and unrelated TEAEs with the same term, the participant will be counted as having related TEAEs.

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

Data listings will be provided for pre-treatment AEs, TEAEs, TEAEs leading to study drug discontinuation, SAEs, and TEAEs that resulted in death.

AE monitoring begins at signing of ICF and ends at the follow-up visit or at the time of early termination/discontinuation procedures.

6.8.2 Other Safety Analysis

6.8.2.1 Vital Signs

Vital signs parameters include temperature, pulse rate, respiration rate, systolic and diastolic blood pressures. In the qualification phase, vital signs will be obtained at screening, Day -1, predose and 2 hours postdose on Day 1, predose and 2 hours postdose on Day 2, and on Day 3 at least 24 hours after Day 2 dose (or at early termination if applicable). In the treatment phase, vital signs will be obtained at Day -1, Day 30 (or at early termination if applicable), and at the following timepoints in all 5 periods: Day 1 predose, Day 1 hour 2, and Day 2 at 24 hours post Day 1 dose.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for vital sign results and change from baseline by treatment and timepoint of collection for each study phase. Baseline is defined as the last assessment including rechecks taken prior to dosing in each period. Postdose unscheduled or recheck assessments will not be used in summaries. Vital sign data will be listed by study phase and participant.

6.8.2.2 12-Lead ECG

ECG results will be listed by study phase and participant.

6.8.2.3 Clinical Laboratory

Clinical laboratory results will be listed by study phase and participant. Values outside the reference ranges will be flagged in listings.

6.8.2.4 C-SSRS

C-SSRS responses will be listed by study phase and participant.

6.8.2.5 Physical Examination

Physical examination abnormalities will be listed by study phase and participant.

6.8.3 Extent of Exposure and Compliance

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

6.9 [redacted]

[redacted]

6.10 Interim Analyses

No interim analysis is planned.

6.11 Data Monitoring Committee/Internal Review Committee

Not applicable.

7.0 REFERENCES

Chen, L, and K R Bonson. 2013. "An Equivalence Test for the Comparison Between a Test Drug and Placebo in Human Abuse Potential Studies." *J Biopham Stat* 23 (2): 294-306.

Daniel, W W. 1990. *Applied nonparametric statistics.* Pacific Grove, CA: Duxbury.

Hollander, Myles, and Douglas A Wolfe. 1999. *Nonparametric Statistical Methods.* Wiley.

Levy-Cooperman, N, K A Schoedel, B Charkraborty, D Blum, and H Cheng. 2016. "Abuse liability assessment of eslicarbazepine acetate in healthy male and female recreational sedative users: A Phase I randomized controlled trial." *Epilepsy Behav.* 61: 63-71.

Schoedel, K A, A Stockis, and E M Sellers. 2018. "Human abuse potential of brivaracetam in healthy recreational central nervous system depressant users." *Epilepsy Behav.* 78: 194-201.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

There are no changes to protocol planned analyses.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

The primary purpose of this SAP amendment is to clarify the methodology of the sign test and to add supplementary analyses for the primary and key secondary endpoints. The table below outlines changes pertinent to statistical analyses.

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
6.7.3.2 Main Analytical Approach	**The calculation of the sign test, and the CI for the median of the paired difference based on the sign test will exclude participants who have zero difference in scores between the 2 treatments (Daniel 1990)**	Text and reference to Daniel 1990 was deleted. New text and reference were added: **Note that the calculation of the p-value of the sign test excludes paired differences in scores that are equal to zero after subtracting the margin from the differences. The calculation of CI does not exclude any paired difference**	Clarify the analytic method and update the source.

		(Hollander and Wolfe 1999). The conclusions will be based on p-values.	
6.7.3.3 Supplementary Analyses	NA	New text added: **Regardless of the main analytic approach taken per section 6.7.3.2, results of the mixed model (including/excluding carryover effects) and paired t-test will be displayed as a supplementary analysis.**	Added supplementary analysis
6.7.4.3 Sensitivity and Supplementary Analyses	**No sensitivity or supplementary analyses are planned.**	New text added: **For key secondary endpoints, regardless of the main analytic approach taken per section 6.7.4.2, results of the mixed model (including/excluding carryover effects) and the paired t-test will be displayed as a supplementary analysis.**	Added supplementary analysis

9.1.1 Definition of Visit Windows

By-timepoint analyses are generally based on nominal timepoints as recorded in the eCRF. Analysis windows will not be used. Results obtained at unscheduled visits will not be included in statistical summaries by timepoint but are included in data listings.

9.2 Analysis Software

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

Signature Page for Statistical Analysis Plan Amendment 2
Title: TAK-935-1012 16-1-9-2 Statistical Analysis Plan Amendment 1 - 2023-07-20

Approval	[redacted] Statistics 14-Aug-2023 15:39:55 GMT+0000

Document Number: TDN-000196973 v1.0