Clinical Study Protocol

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 1.0, 15 March 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.

TAKEDA PHARMACEUTICALS

PROTOCOL

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

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	TAK-935-1012		
IND Number:	133627	**EudraCT Number:**	2018-002484-25
Compound:	Soticlestat		
Date:	15 March 2023	**Version/Amendment Number:**	Amendment 1

Amendment History:

Date	Amendment Number	Amendment Type	Region
15 March 2023	Amendment 1	Substantial	Global
29 August 2022	Initial protocol	Not Applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided in the study manual.

Takeda Development Center–sponsored investigators will be provided with emergency medical contact information cards at discharge or early termination to be carried by each participant.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the study site.

The names and contact information for the medical monitor and responsible medical officer are in the study contact list.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Electronic signatures are provided on the last page of this document.

[redacted], MD Date
[redacted], Soticlestat Program
Neuroscience Therapeutic Area Unit
Takeda

[redacted], PhD Date
Statistical and Quantitative Sciences
Takeda

[redacted], PhD Date
Quantitative Clinical Pharmacology
Takeda

[redacted], MS Date
Neuroscience Therapeutic Area Unit
Takeda

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, prescribing information and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, life, dignity, integrity, confidentiality of personal information, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the investigator (Appendix B).

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 01 Summary of Changes

Protocol Amendment 01 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 01. The primary reason for this amendment is to update the number of anticipated participants to be enrolled into the qualification phase and ultimately randomized into the treatment phase. The numbers of participants anticipated now in qualification and treatment phase are approximately 140 and 65, respectively.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 01			
Summary of Changes Since the Last Version of the Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
1	Section 2.0 STUDY SUMMARY Section 13.3 Determination of Sample Size	Updated projected number of participants to be enrolled (qualification phase) and randomized (treatment phase).	The total number of participants expected to be enrolled and randomized has been increased due to a higher-than-expected number of early terminations.
2	Section 7.5.2 Diet, Fluid, and Activity Control	Updated the language to clarify that the study drug will be administered with water.	Note added to clarify water intake for dosing is excluded from the fasting period before and after dosing.
3	Section 8.1.4 Overdose	Additional condition added to definition of overdose specific to current study.	To clarify that because the study is blinded, ingestion of additional tablets/capsules will be considered an overdose.
4	Section 8.5 Unblinding Procedure	Removed the requirement for providing emergency unblinding envelopes to study site.	As the study site pharmacy holds the randomization schedule for the study, these envelopes were not needed and subsequently not provided. Note: The dispensing pharmacist can unblind participant's treatment allocation without the envolopes.
5	Section 9.1.4 Vital Sign Procedure	Changed heart rate to pulse rate.	To align with schedule of events
6	Table 9.a Clinical Laboratory Tests	Replaced slash (/) with and/or	To clarify that urine drug screen (UDS) is applicable to all or any of the substances mentioned.
7	Section 9.1.9 Documentation of Substance Use History	Updated language to clarify the timeframe for site to collect substance use history.	To resolve uncertainty pertaining to the timeframe to collect substance use history.
8	Section 9.1.9 Documentation of Substance Use History	Added specific quantities for various alcoholic beverages under alcohol history.	Adding definition of alcohol units to the protocol.

Protocol Amendment 01			
Summary of Changes Since the Last Version of the Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
9	Section 9.1.12.2 Female Participants and Their Male Partners	Updated requirement for negative urine human chorionic gonadotropin (hCG) pregnancy test and aligned it with schedule of study procedures.	Women of childbearing potential (WOCBP) who remain confined to the clinical site during the treatment phase need not repeat pregnancy tests before dosing during the treatment phase.
10	Section 9.1.12.3 Contraceptive Methods for Female Participants of Childbearing Potential	Added bilateral tubal ligation as an example of acceptable nonhormonal methods of contraception.	This method of nonhormonal contraception is more commonly used (compared to bilateral occlusion) as a non-hormonal methods of contraception in the United States where this study is being conducted.
11	Table 9.c [redacted]	[redacted]	[redacted]
12	Section: 9.5.4 Follow-up (Final Visit or ET)	Clarified definition of final visit and to align the section with Section 6.1 Study Design. Also clarified that the visit can also be a phone call.	To clarify that all participants even those who early terminate should receive a follow-up call approximately 7 days after their early termination (ET) visit. Clarification regarding phone call added to align with schedule of study procedures.
13	Section 10.1.3 Additional Points to Consider for AEs	Removed stipulation that investigator will define overdose.Added note clarifying that additional tablets or capsules is considered an overdose.	Due to the double-blind nature of the study, removed this requirement and to clarify that ingestion of any additional tablets or capsules would be considered an overdose.
14	Section 13.3 Determination of Sample Size	Updated language to add flexibility for participants who may prematurely discontinue the study.	Clarified that participants who early terminate from the study may be replaced.
15	Appendix A [redacted]	[redacted]	[redacted]

Protocol Amendment 01			
Summary of Changes Since the Last Version of the Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
16	Appendix A	[redacted]	[redacted]
17	Appendix A	[redacted]	[redacted]
18	Appendix A	[redacted]	[redacted]
19	Appendix A	[redacted]	[redacted]

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc	**Compound:** Soticlestat (TAK-935)	
Title of Protocol: 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	**IND No**.: 133627	**EudraCT No**.: 2018-002484-25
Study Number: TAK-935-1012	**Phase:** 1	

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 single oral doses of 2 mg of alprazolam and placebo in healthy adult, nondependent recreational drug users with central nervous system (CNS) depressant experience.

Participants who complete the study will be in the study for approximately 11 weeks (including approximately 5 weeks in the qualification and treatment phases). This study includes:

- Screening phase of up to 4 weeks.
- Qualification phase (4 days).
- Treatment phase (5 periods with at least a 7-day washout between each period).
- Follow-up visit occurring 7 days after last treatment phase period and discharge from the clinical research unit (CRU).

Screening Phase	**Randomization to Sequence Q1 and Q2**	**Sequence**	**Qualification Phase**		**Randomization to Sequence 1 -10**	**Sequence**	**Treatment Phase [a]**					**Followup Phase**
within 28 days of qualification phase			**Day 1**	**Day 2**			**Period 1**	**Period 2**	**Period 3**	**Period 4**	**Period 5**	**Discharge**
			Treatments				**Treatments**					
		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.

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 with 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 pharmacodynamic (PD) and safety assessments will be performed before and after each study drug administration.

Eligible participants who qualify in the qualification phase may be released from the study site and, if they continue to meet eligibility criteria, will enter the 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.

During the treatment phase of the study, participants will receive medication (double-dummy) on each dosing day in a randomized, double-blind, crossover fashion.

Study drug administration during each treatment phase period will occur on the first day 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 terminal disposition phase half-life ($t_{1/2}$), 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, 24*S*-hydroxycholesterol reduction in plasma) returns to baseline slowly but within 7 days (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.

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 depressant experience.

Secondary Objective:

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

[redacted]

Participant Population: Healthy adult, nondependent recreational drug users with CNS depressant experience, aged 18 to 55 years, inclusive.

Number of Participants:	**Number of Sites:**
Qualification phase: Approximately 140 participants will be enrolled into the qualification phase of the study, randomized equally to the 2 qualification sequences. Treatment phase: 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.	1-2 sites in the United States.

Dose Level(s):	**Route of Administration:**
Qualification phase: Alprazolam 2 mg and matching placebo. Treatment phase: Soticlestat 300, 600, 900 mg; alprazolam 2 mg; and corresponding matching placebo.	Oral
Duration of Treatment: Qualfication phase: Two days of treatment (single doses of alprazolam and placebo). Treatment phase: Five days of treatment (single doses of soticlestat 300, 600, 900 mg; alprazolam 2 mg; and placebo).	**Period of Evaluation:** Approximately 11 weeks, which include: • Screening phase - up to 4 weeks. • Qualification phase - 4 days. • At least 4-day washout between the qualification phase and the treatment phase. • Treatment phase - 5 periods with at least a 7-day washout between each period. • Follow-up visit - occurring 7 days after last treatment phase period and discharge from the CRU.

Main Criteria for Inclusion:

- The participant is 18 to 55 years of age, inclusive, at the screening visit.
- The participant is healthy as determined by the investigator.
- Participant is a current CNS depressant user who has used CNS depressants (eg, benzodiazepines, barbiturates, zolpidem, eszopiclone, zopiclone, propofol/fospropofol, gamma-hydroxybutyrate) for recreational, nontherapeutic reasons at least 10 times in their lifetime and at least once in the 12 weeks before screening.
- Participant also must have recreational experience with at least 1 other drug class associated with abuse (eg, opioids, stimulants, cannabinoids, hallucinogens, dissociatives) at least 10 times in their lifetime.

Main Criteria for Exclusion:

Participant has a self-reported history of drug or alcohol dependence (within the past 1 year, except caffeine or nicotine, before the screening visit) and assessed by the investigator at screening visit or has ever participated in a treatment program or rehabilitation (lifetime) for alcohol or substance dependence (other than nicotine or caffeine).

Participant has a positive alcohol breathalyzer or urine drug screen (UDS) for substances of abuse at admission, excluding tetrahydrocannabinol (THC). If a participant presents with a positive UDS, excluding THC, the participant may be rescheduled to repeat the UDS and can only be admitted upon a negative UDS being obtained, excluding THC. Positive THC UDS will be permitted at admission as long as the participant is not impaired at admission, in the clinical judgment of the investigator.

Participants have used any concomitant medications (including prescription and nonprescription medications, herbal remedies, or vitamin supplements) within 7 days (or 5 times the $t_{1/2}$, if known) before the first study drug administration in the qualification phase and throughout the study. Exceptions include:

- Thyroid hormone replacement medication may be permitted if the participant has been on the same stable dose for the immediate 3 months before first dosing in the qualification phase.
- Oral contraceptive is allowed if its use is consistent (ie, no change in oral contraceptive) throughout the study.

The participant has any positive response on the Columbia Suicide Severity Rating Scale (C-SSRS) or has a risk of suicide according to the investigator's judgment based on the assessment of the C-SSRS at screening or baseline or has made a suicide attempt in the previous 12 months before dosing in the qualification phase.

Main Criteria for Evaluation and Analysis

Primary Endpoint:

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

Key Secondary Endpoints, PD:

- 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).

Other Secondary Endpoints, PD:

- 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).

Secondary Endpoint, Safety:

Incidence of treatment-emergent adverse events (TEAEs).

Other Safety Endpoints:

- Clinical laboratory values, vital signs, and electrocardiograms (ECGs).
- Presence of suicidal ideation or behavior based on the C-SSRS responses.

[redacted]

Statistical Considerations:

Analysis Sets:

- Randomized analysis set: All participants who are randomized in the treatment phase.
- 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.
- 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-point difference) for a participant across all treatments (including placebo)
OR

b) E_{max} (positive control) ≤55
OR

c) E_{max} (placebo) - E_{max} (positive control) ≥5.
This analysis set will be used for PD analyses.

PD Analysis: General Considerations:

PD endpoints will only be analyzed or summarized for the treatment phase unless otherwise stated.

For each PD endpoint, the number of participants with nonmissing values, mean, standard error, minimum, first quartile (Ql), 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.

PD Analysis: Primary Endpoint:

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 with placebo (P)?

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

where μ_C and μ_P are the mean Drug Liking VAS E_{max} for alprazolam and placebo, respectively.

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

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

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 with placebo?

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

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.

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

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.

If the variances across treatment groups shows potential heterogeneity, the model will be fitted to allow unequal variances across treatment groups. If non-normality of residuals is detected in the model, a paired t-test or sign test will be used as appropriate for hypothesis testing. If a potential carryover effect is detected then a carryover effect term will be included in the mixed effects model.

PD Analysis: Secondary 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 hypothesis 1 and 2, and 2-sided significance level 0.10 for hypothesis 3.

1. Positive control (alprazolam) (C) versus placebo (P):

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

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

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

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

H_0: $\mu_T - \mu_P = 0$ 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.

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.

Safety Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and characterized as pretreatment and treatment-emergent according to the intake of the study drugs. TEAEs will be summarized by treatment showing the number and percentage of participants who experienced at least 1 TEAE and the number of TEAEs reported. A by-participant adverse event (AE) data listing including reported term, coded term, treatment, severity, and relationship to treatment will be provided. TEAEs leading to discontinuation and SAEs will be listed separately.

Vital signs data will be summarized by study phase and treatment and will be listed by participant. Observed values and changes from baseline will be presented.

Physical examination abnormalities, ECG results, clinical laboratory values, and C-SSRS responses will be listed by participant.

Sample Size Justification:

The qualification phase of the study is based on a 2 × 2 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.

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 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.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform these activities either in full or in partnership with the sponsor.

The study is being funded by Takeda. Payments for the conduct of the study that will be made to the study site (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and sub-investigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and sub-investigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their study site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.

3.2 Principal and Coordinating Investigator(s)

The principal investigator at the single study site has significant knowledge of the study protocol, the study drug, expertise in the therapeutic area, and the conduct of clinical research. The coordinating investigator for the study will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

24HC	24S-hydroxycholesterol
AE	adverse event
ALT	alanine aminotransferase
[redacted]	[redacted]
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time cuve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to last quantifiable concentration
[redacted]	[redacted]
BID	twice daily
Bs	baseline
CDER	Center for Drug Evaluation and Research
CH24H	cholesterol-24 hydroxylase
C_{max}	maximum observed concentration
$C_{max,u}$	unbound C_{max} concentration
CNS	central nervous system
COVID-19	coronavarius disease 2019
CRU	clinical research unit
CSA	Controlled Substances Act
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P-450
DEE	developmental epileptic encephalopathy
DS	Dravet syndrome
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-IV text revision
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
(e)consent	electronic or written consent
eCRF	electronic case report form
EDC	electronic data capture
E_{max}	maximum effect
[redacted]	[redacted]
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
hCG	human chorionic gonadotropin
IB	investigator's brochure

ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	institutional review board
LGS	Lennox-Gastaut syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple-rising dose
MRHD	maximum recommended human dose
NMDA	*N*-methyl-D-aspartate
PD	pharmacodynamic(s)
P-Gp	P-glycoprotein
PK	pharmacokinetic(s)
PTE	pretreatment events
QD	once daily
QTcF	Fridericia-corrected QT interval
rSDV	remote source data verification
SAE	serious adverse event
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
THC	tetrahydrocannabinol
t_{max}	time of first occurrence of C_{max}
UDS	urine drug screen
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WHO	World Health Organization
WOCBP	women of childbearing potential

4.0 INTRODUCTION

4.1 Background

Soticlestat is being developed for the treatment of seizures in patients with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS).

Soticlestat is a potent inhibitor of cholesterol-24 hydroxylase (CH24H) in the brain. Although the exact therapeutic mechanisms of soticlestat still remain to be fully understood, pharmacological modulation of CH24H can potentially alter the function of *N*-methyl-D-aspartate (NMDA) receptors because 24S-hydroxycholesterol (24HC), the metabolic product of CH24H reaction, is known as an endogenous modulator of the NMDA (Paul et al. 2013) receptors. Therefore, soticlestat can be considered an indirect NMDA modulator, which is mediated by reduction of 24HC.

Nonclinical studies have demonstrated that soticlestat modulates glutamatergic signaling and significantly reduces spontaneous seizure in murine models. The phase 2 clinical study TAK-935-2002 (ELEKTRA) showed efficacy of soticlestat in participants with DS or LGS who had seizures that were intractable to current antiseizure medications.

Soticlestat is rapidly absorbed following oral administration with a median time to maximum plasma concentration of 0.5 to 0.75 hours (oral tablets; TAK-935-1005 and TAK-935-1004) and a mean terminal disposition phase half-life ($t_{1/2}$) ranging from 2.6 to 8.7 hours (oral tablets). Exposure to soticlestat increased in a greater than dose-proportional manner over the single-dose range of 200 to 1200 mg (oral tablets; TAK-935-1004) and 15 to 1350 mg (oral solution; TAK-935-101).

The positron emission tomography imaging data showed that the enzyme occupancy increased with increasing dose and plateaued at approximately 93% at 2 hours with 200 mg single dose. The maximum enzyme occupancy of approximately 96% at 2 hours was observed at the 600 mg single dose. Although soticlestat rapidly engages with the CH24H target, maximum reduction of 24HC levels (ie, the pharmacological mediator of soticlestat's effects) was observed at approximately 16 hours postdose after single 50, 200, and 600 mg doses and at approximately 48 hours postdose after single 900 and 1350 mg doses (TAK-935-101 CSR).

In addition, although soticlestat has a relatively short plasma elimination $t_{1/2}$, the pharmacodynamic (PD) effect (ie, reduction of 24HC levels) returned slowly to baseline at 96 hours postdose following single doses (TAK-935-101 CSR). Average change from baseline 24HC during 12 hours at steady-state were simulated at increasing twice daily (BID) doses based on a population pharmacokinetics (PK) and 24HC model of pooled data from phase 1 and phase 2 studies. Simulations with 100, 200, and 300 mg BID indicate that 24HC levels returned to baseline within 7 days after treatment stop (Population PK/24HC Memo dated 16 December 2021).

Since soticlestat is a central nervous system (CNS)–active new molecular entity, Takeda has conducted the agreed nonclinical abuse/dependence evaluation of the compound, as per United States (US) Food and Drug Administration (FDA) guidelines. The nonclinical evaluation of abuse

potential showed that soticlestat did not have any significant 2-dimenisonal structural similarities to Schedule I to V compounds listed in the US Controlled Substances Act or bind to known abuse-related pharmacologic targets at clinicaly relevant concentrations (Investigator's Brochure [IB] Edition 7).

In vivo, soticlestat was not found to produce physical dependence in a rat model of chronic soticlestat dosing and then withdrawal at plasma values that were up to approximately 20-fold the maximum observed concentration (C_{max}) at the maximum recommended human dose (MRHD) of 300 mg BID (Study 8478301).

In addition, soticlestat did not have reinforcing properties in an intravenous (IV) self-administration model in rats at plasma levels of up to 1.4-fold the MRHD (Study 8478298) and did not generalize to the interoceptive cue produced by ketamine in rats at plasma concentrations of up to approximately 7.4-fold the C_{max} at the MRHD (Study 8478299).

Combining studies of phase 1 and the placebo-controlled parts of phase 2 studies, the incidence of abuse related, treatment-emergent adverse events (TEAEs) was 17.9% for soticlestat versus 9.6% for placebo and consisted mostly of dizziness and somnolence. Focusing on abuse-related TEAEs that emerged on Day 1 of treatment, the time most relevant to human abuse, the incidence of abuse-related TEAEs was 4.7% for participants on soticlestat versus 1.8% for participants on placebo (CSRs TAK-935-101, TAK-935-1002, TAK-935-1004, TAK-935-2008 [part A], TAK-935-2001 [part 1] and TAK-935-2002).

There were 3 reports of euphoric mood by participants receiving soticlestat. Although there were 2 cases of euphoric mood within 1 to 2 hours of soticlestat dosing, evaluation of PD parameters for these participants did not show a marked effect on 24HC concentrations at this time, indicating that the effects were unlikely related to soticlestat.

4.2 Rationale for the Proposed Study

As part of the comprehensive assessment of the relative abuse potential of soticlestat, which includes nonclinical and clinical assessments, and in accordance with guidelines provided by FDA and to meet the requirement for regulatory filing and registration, this study will be conducted to provide additional information on the relative abuse potential of soticlestat in healthy adult nondependent recreational drug users with CNS depressant experience.

4.3 Benefit/Risk Profile

In the phase 1b/2a and phase 2 studies completed to date, the safety and tolerability data indicate that soticlestat was generally safe and well tolerated in participants with developmental epileptic encephalopathies (DEEs) at doses up to 300 mg BID (weight-based dosing for <60 kg) with initial dose up-titration.

- To date, Takeda has completed a total of 10 clinical studies including phase 1 single-rising dose (SRD) and multiple-rising dose (MRD) studies in healthy participants and phase 2 studies in DEE and patients with complex regional pain syndrome (CRPS). Overall, soticlestat was safe and well tolerated, and there were no observed dose responses for TEAEs in 2 SRD

studies where the healthy participants were dosed with up to 1350 mg (TAK-935-101) and 1200 mg (Part 1 of TAK-935-1004).

- In the TAK-935-1002 MRD study, where dose up-titration/optimization was not implemented, soticlestat at 300 mg BID and 600 mg once daily (QD) did not appear to be well tolerated by healthy participants due to the emergence of multiple neurological and psychiatric events (reference TAK-935-1002, CSR). These events/TEAEs were all mild except for 1 case of acute psychosis (severe), insomnia (severe), and distractibility (moderate) reported by the same participant. The conditions of the TEAEs were reversible, and all participants recovered. There were no serious adverse events (SAEs). No clear dose-response relationship was observed for any specific TEAE across all dose cohorts.
- All subsequent repeated-dose studies implemented dose up-titration/optimization to the target dose levels of up to 300 mg BID. No individual or population dose-response for safety events have been observed during the dose up-titration/optimization and maintenance periods. Soticlestat has been well tolerated up to 300 mg BID with dose up-titration/optimization without emergence of any new safety issues to date.

This study evaluates 3 different single dose levels, including 300, 600, and 900 mg, all of which were generally safe and well tolerated in phase 1 studies. Further, single doses higher than 900 mg were also safe and well tolerated in phase 1 studies, as described above.

This is an inpatient study, and the participants will be closely monitored for the emergence of any adverse events (AEs), which will be managed at the earliest as required.

More information about the known and expected benefits and risks of soticlestat may be found in the current edition of the IB. In this healthy adult nondependent recreational drug user with CNS depressant experience population, no beneficial effects are expected; however, this study will help evaluate the relative abuse potential of 3 different single dose levels of soticlestat compared with placebo and positive control alprazolam in humans and add further data to the profile of overall benefit-risk in DS and LGS.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 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 depressant experience.

5.1.2 Secondary Objectives

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

5.1.3 [redacted]

[redacted]

5.2 Estimands

Not applicable.

5.3 Endpoints

5.3.1 Primary Endpoint

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

5.3.2 Secondary Endpoints, PD

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).

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).

5.3.3 Secondary Endpoint, Safety

Incidence of TEAEs.

5.3.4 Other Safety Endpoints

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

5.3.5 [redacted]

[redacted]

[redacted]

5.3.6 [redacted]

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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 with 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 before and after each study drug administration.

Eligible participants who qualify in the qualification phase (criteria described in Section 7.3) may be released from the study site and, if they 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 before randomizing these participants and continue to monitor for SAEs 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 before 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 Table 6.a.

The treatment phase will include 5 treatment periods as described in the Table 6.a.

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 Table 6.a [redacted]

Table 6.a Schematic of Study Design

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).

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Dose Rationale

This study is undertaken to assess the relative human abuse potential of a single dose of soticlestat at the highest proposed therapeutic level of 300 mg administered BID and supratherapeutic dose levels (600 and 900 mg).

Three dose levels are chosen to determine dose response, if any. A supratherapeutic dose of 600 and 900 mg will represent an adequate 2- and 3-fold difference from the highest proposed therapeutic dose level, respectively (FDA, Guidance for Industry Assessment of Abuse Potential of Drugs, January, 2017).

The supratherapeutic dose levels of 600 and 900 mg also present >2- and >3-fold difference from the C_{max} and area under the concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{last}) and from time 0 to infinity (AUC_{∞}) than the highest proposed therapeutic dose level of 300 mg, respectively, as exposure of soticlestat generally increased more than dose proportionally from 200 to 1200 mg (oral tablets; TAK-935-1004 CSR). In the clinical setting soticlestat is administered as BID doses and no clinically meaningful accumulations were observed following multiple BID doses (accumulation ratio 1.05; TAK-935-1004 CSR).

In addition, measured CH24H enzyme occupancy increased with increasing dose and plateaued at 200 mg single dose (approximately 93% at 2 hours; TAK-935-1003 CSR). The maximum enzyme occupancy was achieved at a 600 mg single dose, the highest dose tested in the study (approximately 96% at 2 hours).

Soticlestat was safe and well tolerated when administered as a single dose up to 1350 mg (TAK-935-101 CSR). In vitro screening of soticlestat against a panel of more than 100 known molecular targets such as receptors, ion channels and enzymes revealed no relevant off-target activity at tested concentrations (3735 ng/mL [reports TAK-935-10077, 100054231 and OTI-20-21]) higher than the unbound C_{max} concentration ($C_{max,u}$) associated with a single 1350 mg dose [C_{max} 7953 ng/mL (TAK-935-101 CSR); $C_{max,u}$ 2338 ng/mL assumes 70.6% bound (TAK-935-1005)].

6.2.2 Rationale for Active Comparator

Alprazolam 2 mg has been selected as the active comparator based on the following:

- According to FDA guidance (US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER): Assessment of Abuse Potential of Drugs, January 2017), ideally, "the positive control should be an FDA-approved drug that is pharmacologically similar to the test drug and scheduled under the [Controlled Substances Act] CSA."
- Soticlestat is a novel compound that is not pharmacologically similar to any existing drugs of abuse. Although soticlestat may exert its pharmacological action through indirect effects on NMDA receptors, it did not generalize to ketamine in a rat drug discrimination study,

indicating that it does not share subjective similarities to ketamine, a prototypic NMDA receptor antagonist. For a compound with novel mechanism of action, such as soticlestat, FDA recommended an appropriate positive control of a depressant listed under schedule IV of the CSA (eg, a benzodiazepine).

- Soticlestat produced no abuse-like behavioral effects in rats or dogs, eg, excitation, hyperactivity, stereotypy, somnolence, sedation, or "wetdog" shakes, at doses ≤500 mg/kg (juvenile rats), ≤300 mg/kg (adult rats) or ≤30 mg/kg (dogs). In humans, acute and chronic administration of soticlestat in patients and healthy participants did not produce effects (ie, sedative, stimulant, mood-elevating, or hallucinogenic effects) consistent with those of abused drugs, even when administered at supratherapeutic doses.
- Overall, the data with soticlestat do not suggest any particular class of drugs of abuse as an ideal positive control; therefore, a benzodiazepine has been selected as a positive control, as these have some similarities in therapeutic effects to soticlestat (ie, anticonvulsant effects) and a similar potential general indication (ie, treatment of seizure disorders).
- Benzodiazepines, and more specifically alprazolam, has been used, as positive control, in a number of prior human abuse potential studies of anti-epileptic drugs with novel pharmacology (Levy-Cooperman et al. 2016; Schoedel et al. 2017; Schoedel et al. 2018a; Schoedel et al. 2018b).
- Because of the flat dose-response observed with benzodiazepines on subjective measures such as Drug Liking (Levy-Cooperman et al. 2016), only 1 dose will be included in the current study. The 2 mg dose of alprazolam was selected because it has been used in previous human abuse potential studies mentioned above and is not expected to produce the sedation often observed with the higher 3 mg dose, which may interfere with the collection of subjective PD measures.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination (ET) of the study.

- New information or other evaluation regarding the safety or PD of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit profile is no longer acceptable for participants participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Site

A study site may be terminated prematurely or suspended if the study site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for ET or suspension will be provided by the sponsor; the procedure will be followed by the study site during the course of termination or study suspension.

6.3.4 Duration of an Individual Participant's Study Participation

Participants who complete the study* will be in the study for approximately 11 weeks (including approximately 5 weeks (in the qualification and treatment phases).

This study includes:

- Screening phase of up to 4 weeks.
- Qualification phase (4 days).
- Treatment phase (5 periods with at least a 7 day washout between each period).†
- Follow-up visit occurring 7 days after last treatment phase period and discharge from the CRU.

6.3.5 End of Study/Study Completion Definition

The end of the study for an individual participant is defined as the last protocol-specified contact with that participant. The overall end of the study is defined as the last protocol-specified contact with the last participant ongoing in the study.

6.4 Posttrial Access

Not applicable in this healthy participant study.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

All entry criteria, including test results, need to be confirmed before entry into the study.

7.1 Inclusion Criteria

Participant eligibility is determined according to the following criteria before entry into the study:

1. The participant is willing and able to understand and fully comply with study procedures and requirements (including digital tools and applications), in the opinion of the investigator.
2. The participant has provided written, signed, and dated informed consent and any required privacy authorization before the initiation of any study procedures.
3. The participant is 18 to 55 years of age, inclusive, at the screening visit.

* The site may extend the participant's participation by extending the duration between qualification phase and Treatment phase to maximize site efficiency/scheduling.

† At minimum, there will be a 4-day washout between the qualification phase and the treatment phase.

4. The participant is healthy as determined by the investigator. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, complete physical examination, vital signs, 12-lead ECG, and clinical laboratory tests.
5. Participant is a current CNS depressant user who has used CNS depressants (eg, benzodiazepines, barbiturates, zolpidem, eszopiclone, zopiclone, propofol/fospropofol, gamma-hydroxybutyrate) for recreational, nontherapeutic reasons at least 10 times in their lifetime and at least once in the 12 weeks before screening. Participant must also have recreational experience with at least 1 other drug class associated with abuse (eg, opioids, stimulants, cannabinoids, hallucinogens, dissociatives) at least 10 times in their lifetime.
6. The participant has a body mass index of 18.5 to 35.0 kg/m^2, inclusive, and a minimum body weight of 50.0 kg at screening.
7. Female participants of childbearing potential (defined in Section 9.1.12.2) must have a negative pregnancy test at screening and agree to use an effective or highly effective method of birth control, as listed in Section 9.1.12.3, during the study and for 32 days following the last dose of study drug.

7.2 Exclusion Criteria

Any participant who meets any of the following criteria will not qualify for entry into the study:

1. The participant has a self-reported history of drug or alcohol dependence (within the past 1 year, except caffeine or nicotine, before the screening visit) as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV text revision (DSM-IV-TR; [American Psychiatric Association, 2000]) and assessed by the investigator at screening visit or has ever participated in a treatment program or rehabilitation (lifetime) for alcohol or substance dependence (other than nicotine or caffeine).
2. The participant has a positive alcohol breathalyzer or urine drug screen (UDS) for substances of abuse at admission, excluding tetrahydrocannabinol (THC). If a participant presents with a positive UDS, excluding THC, the participant may be rescheduled to repeat the UDS and can only be admitted upon a negative UDS being obtained, excluding THC. Positive THC UDS will be permitted at admission as long as the participant is not impaired at admission, in the clinical judgment of the investigator.
3. The participant is a heavy smoker or user of other types of nicotine products (>20 cigarettes equivalent per day).
4. The participant is unable to abstain from smoking for at least 2 hours before and at least 8 hours after dosing.
5. The participant consumes excessive amounts, defined as greater than 4 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
6. The participant has used any concomitant medications (including prescription and nonprescription medications, herbal remedies, or vitamin supplements) within 14 days (or 5

times the $t_{1/2}$, if known) before the first study drug administration in the qualification phase and throughout the study.

Exceptions include:

- Thyroid hormone replacement medication may be permitted if the participant has been on the same stable dose for the immediate 3 months before first dosing in the qualfication phase.
- Oral contraceptive is allowed if its use is consistent (ie, no change in oral contraceptives) throughout the study

7. The participant has used any drug known to be a significant inducer of cytochrome P-450 (CYP) 3A, CYP2C19, uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9 or UGT2B4 enzymes, and/or P-glycoprotein (P-gp), including St. John's wort, within 28 days before the first dose in the qualification phase. (Appropriate sources [eg, Flockhart Table] will be consulted to confirm lack of PK-PD interaction with study drug.)
8. The participant has received:
   - An investigational drug within 5 × the known elimination $t_{1/2}$, or, if the $t_{1/2}$ is unknown, within 30 days of first anticipated study drug administration in the qualification phase.
   - An investigational biologic product within 90 days before the first anticipated study drug administration in the qualification phase.
9. The participant took part in a previous soticlestat clinical study.
10. The participant has a history or current presence of any clinically significant medical conditions, which in the opinion of the Investigator would jeopardize the safety of the participant or the validity of the study results (eg, any major cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, ophthalmologic, immunologic, dermatologic, neurologic, oncologic, musculoskeletal, psychiatric disease [including an established diagnosis of an underlying psychotic illness], or clinical assessment abnormality [as found in physical examination, medical history, 12-lead ECG, vital signs, or clinical laboratory values]).
11. The participant has a history or presence of any of the following specific ECG abnormalities:
    - Established QT prolongation.
    - Atrial fibrillation.
    - Long QT syndrome.
    - Torsades de pointes.
    - Bradyarrhythmia.
    - Uncompensated heart failure.

- Any 12-lead ECG with repeated demonstration of Fridericia-corrected QT interval (QTcF) ≥470 msec in female participants, ≥450 msec in male participants, and/or a QRS interval ≥120 msec at screening.

12. The participant has a family history (anamnesis or first degree relative with history) of unexplained sudden death or long QT syndrome.
13. The participant has evidence of clinically significant hepatic or renal impairment including (but not limited to) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2× the upper limit of normal (ULN), or clinically significant renal impairment as shown by estimated creatinine clearance < 80 mL/min (using the Cockcroft-Gault equation).
14. The participant has a history of severe allergic reaction (including anaphylaxis) to any food, medications, or bee sting, or a history of previous status asthmaticus.
15. The participant has a history of allergy or hypersensitivity to alprazolam or related drugs.
16. The participant tests positive for hepatitis B, hepatitis C, or HIV at the screening visit.
17. The participant has had any significant illness, of any nature, including coronavirus disease 2019 (COVID-19) –related fever and symptoms, requiring hospitalization, emergency treatment, or isolation (community mandated quarantine) within 4 weeks before screening or during the study and as determined by the investigator.
18. The participant has donated or lost more than 500 mL of whole blood within 30 days preceding anticipated entry into the treatment phase.
19. The participant is currently pregnant or breastfeeding.
20. The participant has any positive response on the C-SSRS or has a risk of suicide according to the investigator's judgment based on the assessment of the C-SSRS or has made a suicide attempt in the previous 12 months.
21. The participant is considered unsuitable or unlikely to comply with the study protocol for any reason by the investigator.

7.3 Qualification Criteria (Applicable to Passing Qualification Phase)

Participants will be required to meet all of the following qualification criteria to be eligible to enter the treatment phase:

1. The participant continues to meet all of the inclusion criteria and none of the exclusion criteria above.
2. The participant satisfactorily completes the qualification phase.
3. On the assessment of drug liking ("at the moment" Drug Liking VAS):
   - The participant's E_{max} on "at the moment" Drug Liking VAS in response to alprazolam is numerically ≥15 points higher than that of placebo, and the participant has an E_{max} of ≥65 points with alprazolam.

- The participant has an acceptable placebo response based on the Drug Liking VAS, defined as a E_{max} between 40 and 60 points (ie, a score considered neutral on the scale, meaning neither like nor dislike), inclusive.
- The participant has acceptable overall responses to alprazolam and placebo on the subjective measures, as judged by the investigator or designee.

4. The safety data available following study drug administration suggest that the participant will be able to tolerate the alprazolam 2 mg dose planned for the treatment phase, as judged by the investigator, including no missing PD assessments within 4 hours of drug administration.
5. The participant's general behavior suggests that the participant could successfully complete the study, as judged by the investigator.

7.4 Excluded Medications

All nonstudy medications, including prescription, over-the-counter, herbal therapies, or vitamin supplements used by the participant will be documented for the 30 days before screening and throughout the study. The investigator will determine if the prior/concomitant medication(s) affect the participant's eligibility to participate or continue to participate in the study. The following restrictions on concomitant medications will be in place during the study:

- The use of prescription drugs (except hormonal contraceptives and hormone replacement therapy), vitamins, or mineral supplements and natural health products (eg, herbal remedies) will be restricted for at least 14 days (or 5 times the $t_{1/2}$ of the drug, if known) before first study drug administration in the qualification phase and throughout the study (exceptions include alprazolam administered as positive control and thyroid hormone replacement medication as long as the participant has been on the same stable dose for the immediate 3 months before the first study drug administration in the qualification phase).
- The use of over-the-counter medications (except acetaminophen or ibuprofen) will be restricted for at least 14 days (or 5-times the $t_{1/2}$ of the drug, if known) before first study drug administration in the qualification phase and throughout the study.
- The use of investigational drugs will be restricted for 5 × the known $t_{1/2}$ or, if the $t_{1/2}$ is unknown, for 30 days, before the first anticipated study drug administration in the qualification phase and throughout the study.
- The use of investigational biologic products will be restricted for 90 days, before the first anticipated study drug administration in the qualification phase and throughout the study.
- Any drugs known to be significant inducers of CYP3A, CYP2C19, UGT1A9, or UGT2B4 enzymes and/or P-gp, including St. John's wort, will be restricted within 28 days before the first study drug administration in the qualification phase and throughout the study. Appropriate sources (eg, Flockhart Table) will be consulted to confirm lack of PK/PD interaction with study drug.

7.5 On-Study Restrictions

Participants will enter the study site the day before dosing (Day -1) of the qualification phase.

In addition to the inclusion/exclusion criteria, the participant must agree to abide by the study restrictions listed in Sections 7.5.1 and 7.5.2.

7.5.1 Alcohol and Drug Use

- Participants will be asked to abstain from alcohol for 24 hours before each study visit. If a participant presents with a positive breath alcohol test at any visit after the screening visit, the participant may be rescheduled to repeat the breathalyzer test at the respective admission visit and can only be admitted upon a negative result being obtained.
- Participants will be asked to abstain from recreational drug use/experience throughout the study, from screening until after the follow-up visit or ET. Abstinence will be confirmed via UDS (at screening, at admission [Day -1] to the qualification phase and at check-in for the treatment phase. (Note: If participant is released at investigator discretion from the clinic during the treatment phase [during washout], participant will be checked in again upon readmittance to the clinic for the next treatment period.)
  - If a participant presents with a positive UDS at screening, investigator may determine if the screening visit may continue that day or if it should be continued another day. In these cases, investigator may conduct a screening visit over multiple days. In these cases,] at investigator discretion, screening procedures may be repeated.
  - If a participant presents with a positive UDS (excluding THC) at admission to the qualification phase, the participant will not be admitted but may, at the discretion of the investigator, repeat the UDS at a later date and be admitted to the qualification phase upon a negative UDS being obtained. (Note: In case of discharge between qualification phase and treatment phase same conditions apply.)
  - Positive THC UDS will be permitted at admission to the qualification phase as long as the participant is not impaired at admission, in the clinical judgment of the investigator. Participants will be advised that no THC use is permitted during the inpatient qualification or treatment phases.

7.5.2 Diet, Fluid, and Activity Control

- Participants will be required to fast (abstain from food) for at least 8 hours before dosing and for at least 4 hours postdose on the day of dosing. Water will be permitted ad libitum except for approximately 1 hour before dosing and for approximately 1 hour postdose (except water provided with each dosing). Note: Study drug will be administered with approximately 240 ml of water. If additional water is needed for a participant to ingest the study drug, up to 50 ml of additional water may be provided.
- Participants will be asked to abstain from strenuous physical activity for 48 hours before admission, and during inpatient stays at the study site.

- Participants will be asked to abstain from the following foods from 1 week before admission to the qualification phase until after the follow-up visit or ET:
  - Grapefruit, pomegranate, pomelo, and star fruit and their juices/products.
  - Poppy seeds and Seville oranges and foods containing them (eg, orange marmalade).
  - Drinks/foods containing quinine (eg, tonic water).
- Participants will be asked to refrain from blood donation from screening until 30 days after the last study drug administration.
- Participants will be asked not to consume more than 4 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day from 1 week before admission to the qualification phase until after the follow-up visit or ET. Participants will not be permitted to consume caffeine-containing beverages during inpatient stays at the study site.
- Participants will be required to abstain from smoking or vaping for at least 2 hours before and 8 hours after dosing on the day of dosing in the inpatient qualification phase and treatment phase sequences. Smoking or vaping will be permitted at short breaks after at least the 8-hour postdose procedures, at the discretion of the study site staff. Participants will not be permitted to use other nicotine-containing products (including nicotine topical patches, nicotine gum, or nicotine lozenges) during the inpatient periods.
- Participants will be required to follow the informed consent form (ICF) and the clinic code of conduct.

7.6 Criteria for Discontinuation or Withdrawal of a Participant

A participant is free to withdraw his/her consent and discontinue participation in the study at any time for any reason.

The primary reason for discontinuation or withdrawal of the participant from the study or study drug should be recorded in the electronic case report form (eCRF) using the categories listed below. For screen failure participants, refer to Section 9.1.14.

- Withdrawal by participant.
- Withdrawal of consent.
- Failure to meet continuation criteria.
- Protocol violation:
  - Noncompliance with study drug or study schedule.
  - Use of unacceptable concomitant medication(s).
  - Use of prohibited substances (positive THC UDS will be permitted at admission to the qualification phase as long as the participant is not impaired at admission, in the clinical judgment of the investigator).

  - Other major protocol violation.

- AE.
- Physician decision.
- Pregnancy.
- Study terminated by sponsor or study site terminated by sponsor.
- Lost to follow-up.
- Other.

The investigator must maintain a record of all participants who discontinue from the study before completion; the reason(s) for study discontinuation will be documented. In the event that a participant chooses to withdraw from the study, the investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal, if possible, although the participant is not obligated to provide such a reason.

In the event that a participant is discontinued while at the study site, the ET procedures shown in [redacted] should be performed before discharge from the study site. For any case of early discontinuation (whether or not the participant is at the study site), the investigator should ask the participant to participate in the follow-up visit procedures, provided that the participant has not withdrawn consent for those procedures. If a participant refuses to complete ET and/or the follow-up procedures, this information will be recorded.

7.7 Procedures for Discontinuation or Withdrawal of a Participant

The investigator may discontinue a participant's study participation at any time during the study when the participant meets the study discontinuation criteria described in Section 7.6. In addition, a participant may discontinue his or her participation without giving a reason at any time during the study. Should a participant's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the ET visit.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling of Study Drug

In this protocol, the term study drug refers to all or any of the drugs defined below.

Investigational product: soticlestat 300, 600, or 900 mg orally administered via 100 mg immediate release tablets or matching placebo.

Reference therapy: overencapsulated alprazolam 2 mg or matching placebo.

Study drug will be administered in a double-blind, double-dummy manner with the oral doses of soticlestat or matching placebo and overencapsulated alprazolam 2 mg or matching placebo administered at each treatment period in the treatment phase.

The sponsor will supply study site(s) with soticlestat (TAK-935) 100 mg tablets, and placebo for match 100 mg tablets. Soticlestat 300 mg tablets may be used instead of 100 mg if bioequivalence is demonstrated in an ongoing BE study TAK-935-1014.‡

Study drug will be supplied in high-density polyethylene bottles with induction seal and child-resistant caps. Each bottle will contain a label that includes pertinent study information and caution statements. For more information on the study drug, please see the study pharmacy manual.

Soticlestat clinical study material will be labeled according to the country's regulatory requirements. Soticlestat and placebo will be provided in open-label configuration, and unblinded study site staff will prepare blinded dosing before administration to participants.

Alprazolam 2 mg and matching placebo will be compounded and supplied for use in this protocol. Instructions for preparation of overencapsulated alprazolam 2 mg and matching placebo can be found in the pharmacy manual.

8.1.2 Storage

Sponsor-supplied study drug must be kept in an appropriate, limited-access, secure place until it is dispensed or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day.

Please refer to the pharmacy manual for additional information related to the study drug. In instances where the protocol and pharmacy manual text conflict, the pharmacy manual text shall supersede the text in the protocol.

Site staff should follow their internal processes for managing, storing and dispensing controlled-substances.

8.1.3 Dose and Regimen

Route of administration: oral.

Dose regimen: single dose, once on Day 1 of each treatment period.

Duration of evaluation and treatment: Participants who complete the study will be in the study for approximately 11 weeks (including approximately 5 weeks in the qualification and treatment phases combined).

This study includes:

- Screening phase of up to 4 weeks.

‡ Protocol will be updated accordingly.

- Qualification phase (4 days).
- Treatment phase (5 periods with 7-day washout between each study drug administration).[§]
- Follow-up visit occurring 7 days after last treatment period and discharge from the CRU.

Table 8.a describes the dose and tablet/capsule count that will be provided to each group.

Table 8.a Treatment Description

Treatment	Soticlestat (100 mg)	Placebo for Soticlestat (100 mg) [a]	Alprazolam [b] (2 mg)	Placebo for Alprazolam (2 mg) [c]
	Number of Tablets/capsules			
A	3	6	0	1
B	6	3	0	1
C	9	0	0	1
D	0	9	1	0
E	0	9	0	1

[a] Placebo that matches 100 mg soticlestat tablets.
[b] Overencapsulated alprazolam.
[c] Placebo that matches overencapsulated alprazolam 2 mg.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study participant, at a dose above that which is assigned to that individual participant according to the study protocol.

Note: Because of the double-blind nature of the study, any additional tablets or capsules ingested at a dosing event will be considered an overdose during the period in which the study is blinded. Investigator to refer to Section 8.5 for decisions regarding unblinding for medical treatment.

All cases of overdose (with or without associated AEs) will be documented. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.1.4.

In the event of drug overdose, the participant should be treated symptomatically.

§ At minimum, there will be a 4-day washout between the qualification phase and the treatment phase.

8.2 Study Drug Assignment and Dispensing Procedures

8.2.1 Assignment of Participant Identification Number

A unique 8-digit participant identification number (participant number) will be assigned to each participant at the time that informed consent is explained; this participant number will be used throughout the study.

8.2.2 Study Drug Assignment

Each participant will be assigned a treatment sequence in each double-blind phase (ie, 1 qualification phase and 1 treatment phase), in accordance with the randomization schedule (refer to Section 6.1).

Refer to the study manual for details concerning sample tracking.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization table/schedule and will provide it to the unblinded study site staff (eg, pharmacist) before the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

The qualification phase of this study will be double-blind. The treatment phase of the study will be double-blind and double dummy; the investigator and participants are blinded to treatment assignment. The study drug will be provided to the site as soticlestat 100 mg tablets and matching placebo tablets in an unblinded manner. Blinding of treatment will be performed by the unblinded study site staff.

8.4 Study Drug Blind Maintenance

The study drug blind is maintained through a randomization schedule held by the dispensing pharmacist. The study drug blind will be maintained for persons responsible for the ongoing conduct of the study (monitors, investigators, etc) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. The treatment phase blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the participant. The sponsor or designee must be notified as soon as possible if the blind is broken.

Since the maintenance of the blind may be compromised because of results from drug concentrations and/or pharmacodynamics assessments, such results should not be disclosed before blind breaking. In the event that results must be reported to the investigator before breaking the blind, all efforts should be made to maintain the blind (eg, as changing a medication identification number in order to avoid identification of participants by the laboratory site personnel).

8.5 Unblinding Procedure

If the participant is found to be not eligible for the qualification phase, the investigator should record the primary reason for failure on the applicable eCRF.

A group of participants that start the qualification phase on the same day will be considered a cohort for unblinding purposes. Upon completion of each qualification phase cohort, the randomization codes for these participants will be unblinded (site), and the eligibility of participants to participate in the treatment phase will be assessed as described in Section 7.3.

Any other instance of unblinding should only be considered for the safety of the participant. The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the participant. All study assessments and causality assessment should be performed, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor and the Takeda trial clinician should be contacted before the study drug blind is broken to discuss the need for unblinding. If unblinding is deemed necessary by the investigator, the investigator can unblind the participant's treatment allocation by contacting the dispensing pharmacist.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any study site personnel are unblinded, study drug must be stopped immediately and the participant must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the study site before being returned to the sponsor or designee, or destroyed by the site where allowed by institutional process and as per sponsor instructions. Any remaining supplies there were purchased by site will be destroyed, as appropriate, by the site.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to participants enrolled in the study. To document appropriate use of sponsor-supplied drug (soticlestat tablets or matching placebo), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the study site, study site inventory, dispensation and use by each participant, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and emailing as per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs (soticlestat and matching placebo) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to, the following requirements:

- If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.
- The investigator or designee must record the current inventory of all sponsor-supplied drugs (soticlestat) on a sponsor-approved drug accountability log.
- All study drug not returned to the study site by a participant must be investigated by the study site and appropriately documented on the drug accountability log.
- Before study site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. Destruction may be completed by the study site after full accountability is completed with sponsor preapproval. The study site must have destruction procedures in place and be able to supply a "Certificate of Destruction" or similar document. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.
- The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the study site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.
- In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor supplied drugs may be relabeled with the new expiry date at that study site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the study site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, participants are to be assessed by the same investigator or study site personnel whenever possible. [redacted]

9.1.1 Informed (e)Consent Procedure

Informed electronic or written consent ([e]consent) must be obtained before the participant enters into the study and before any protocol-directed procedures are performed.

A unique participant identification number (participant number) will be assigned to each participant at the time that informed (e)consent is obtained; this participant number will be used throughout the study.

Participants consenting via (e)consent, where available, will electronically sign consent forms (paper consent forms will be used instead if required by local regulations).

(e)consent provides the same information as written consent forms, but in an electronic format that may include multimedia components. (e)consent does not replace the important discussion between the participants and study site staff or investigator. Regardless of the consent format—written or (e)consent—the study site is responsible for the consenting process. The requirements of informed consent are described in Section 15.2.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, and race as described by the participant at screening.

Medical history to be obtained will include determining whether the participant has any significant conditions that resolved at or before signing informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.10).

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

9.1.3 Weight and Height

Weight and height will be measured while the participant is wearing indoor clothing and with shoes off. If unable to obtain height or weight, data may be collected from other sources (eg, medical records). The investigator must record in the source document the reason for not obtaining height or weight (eg, the participant is in a wheelchair).

The values should be reported to 1 decimal place by rounding.

9.1.4 Vital Sign Procedure

The following vital signs will be recorded [redacted]: systolic and diastolic blood pressure (mm Hg), pulse rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C or °F). If clinically significant vital sign changes from screening/baseline are noted, the changes will be documented as AEs in the AE eCRF. Screening/baseline events will be documented in the medical history eCRF. Clinical significance is defined as any variation in vital signs that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the participant until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.5 ECG Procedure

For each participant, 12-lead digital ECGs will be collected [redacted] Participants must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed, when needed to ensure high-quality recordings.

ECGs will initially be interpreted by a qualified physician (the investigator or qualified designee) at the study site as soon as possible after the time of ECG collection, and ideally while the participant is still present at the study site, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the participant will be assessed by the investigator for symptoms (eg, palpitations, near syncope, syncope) and to determine whether the participant can continue in the study, and the medical monitor or the sponsor should be contacted. The investigator or qualified designee is responsible for determining if any change in participant's management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Any clinically significant finding that was not present at baseline will be reported and discussed with the medical monitor or the sponsor. When there are differences in ECG interpretation between the investigator (or qualified designee) and the study site/local cardiologist, the investigator (or qualified designee's) interpretation will be used for study entry and immediate participant management. The investigator (or qualified designee) must document his/her review of the ECGs printed at the time of collection.

9.1.6 Physical Examination Procedure

A physical examination will be performed [redacted]. A full examination will include the following assessments: eyes; ears; nose; throat; cardiovascular system; respiratory system; gastrointestinal system; dermatologic system; musculoskeletal system; extremities; nervous system; lymph nodes; and other.

If clinically significant changes from screening/baseline are noted, the changes will be documented as AEs in the AE eCRF. Screening/baseline events will be documented in the medical history eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the participant until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

9.1.7 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and specimen handling will be given in the laboratory manual.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Erythrocytes	Sodium	pH
Hemoglobin	Potassium	Protein
Hematocrit	Total bilirubin	Glucose
	Direct bilirubin	Ketones
Red blood cell indices	Indirect bilirubin	Bilirubin
Mean corpuscular volume	Alkaline phosphatase	Erythrocytes
Mean corpuscular hemoglobin	ALT	Leukocyte esterase
Mean corpuscular hemoglobin	AST	Nitrite
concentration	Gamma glutamyl transferase (-)	Urobilinogen
Red cell distribution width	Blood urea nitrogen	Calcium
	Creatinine [a]	Calcium/creatinine
White blood cell count and differential	Urea	Microscopy [c]
Neutrophils, segmented	Calcium	
Lymphocytes	Phosphate	
Monocytes	Glucose	
Eosinophils	Albumin	
Basophils	Protein	
Platelets	Carbon dioxide	
Mean platelet volume	Magnesium	
	Chloride	
	Alpha 1-acid glycoprotein (baseline only) [b]	

Swab test

Severe acute respiratory syndrome coronavirus 2

Other Serum

HIV
Hepatitis B virus surface antigen
Hepatitis B core antibody
Hepatitis C virus antibody

Female participants only:

Beta human chorionic gonadotropin, for pregnancy (WOCBP only)
FSH, if menopause is suspected

Other Urine

UDS for alcohol, if available or a breath test, amphetamines, barbiturates, benzodiazepines, buprenorphineand/or metabolite, cannabinoids/THC, cocaine and/or metabolites, 3-methoxy-4,5-methylenedioxyamphetamine, methadoneand/or metabolite, opiates, oxycodone and/or oxymorphone, phencyclidine. Note: for any UDS after taking the first dose of study drug exclude benzodiazepines.

Female participants only:

Beta human chorionic gonadotropin, for pregnancy (WOCBP only)

ALT: alanine aminotransferase: AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; THC: tetrahydrocannabinol; UDS; urine drug screen; WOCBP: women of child-bearing potential.
[a] Site to calculate the creatinine clearance only at screening visit for inclusion criteria.
[b] Collected at baseline; however, results are not required to assess participant eligibility.
[c] If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

The laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of the laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. [redacted]

As in routine practice, the investigators should use their medical judgment when assessing clinical significance. Clinical significance is defined as any variation in laboratory measurements which has medical relevance, and which results in a change in medical care. If clinically significant laboratory changes from baseline are noted, the changes will be documented as AEs in the eCRF. The investigator will also assess the relationship to study drug for all clinically significant out of range values. The investigator will continue to monitor the participant with additional laboratory assessments until: (1) values have reached normal range and/or baseline, or (2) in the judgment of the investigator, out of range values are not related to the administration of study drug or other protocol-specific procedures.

If participants experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma glutamyltransferase [GGT], and international normalized ratio [INR]) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 10.3.2 for the appropriate guidance on reporting abnormal liver function tests.)

If ALT or AST remains elevated >3 times the ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant participant details and possible alternative etiologies. The abnormality should be recorded as an AE (refer to Section 10.2.1).

Serum alpha 1-acid glycoprotein levels will be evaluated as part of the laboratory serum chemistry panel at baseline only.

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.8 Documentation of Concomitant Medications

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.

Concomitant medications will be coded using the WHO Drug Dictionary. A by-participant listing of concomitant medications will include all medications (including vaccinations) taken during the study regardless of the timing for the start of the medication. All medications started and stopped before the administration of the study drug will be included in the data but will be identified as "prior" in the listing.

The list of excluded medications is provided in Section 7.4.

9.1.9 Documentation of Substance Use History

A history of all drugs used for recreational/nonmedicinal 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.

DSM-IV-TR modules will be included as a part of the recreational drug/alcohol use history and used to screen for alcohol and substance dependence.

9.1.10 Documentation of Concurrent Medical Conditions

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.

9.1.11 Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed by use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, participant endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) (Posner et al. 2011).

The versions of the C-SSRS used for all participants in this inpatient study will be the screening/baseline and Since-Last-Visit C-SSRS. When administering the screening/baseline version, both lifetime and within the last 12 months will be assessed.

Study staff trained in the administration of the C-SSRS will assess participant suicidality using the C-SSRS. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator.

If a participant exhibits signs of suicidal ideation or behavior as per the clinical judgement of the investigator, the participant will be withdrawn from the study as described in Section 7.7. With the identification of positive symptoms of depression and suicidal ideation, the participant will be referred for professional psychiatric assessment and necessary follow-up.

9.1.12 Contraception and Pregnancy Avoidance Procedure

9.1.12.1 Male Participants and Their Female Partners

Male participants who participate in the study are not required to use barrier contraception. Donation of sperm is not allowed during the study and within 90 days following the last administration of the study drug.

9.1.12.2 Female Participants and Their Male Partners

Pregnancy testing at screening, admission to the qualification phase (before receiving any study drug), admission to the treatment phase, and the participant's last clinic visit will be processed using the local laboratory. Additional pregnancy tests (serum or urine) may be performed throughout the study at the investigator's discretion.

Please refer to Section 7.1 for inclusion criteria for detailed contraception requirements.

The following definitions apply for contraception and pregnancy avoidance procedures.

A woman is considered a woman of child-bearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Female participants of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at screening and at the end of treatment They must have a negative urine hCG pregnancy test before dosing on Day -1 of the qualification phase and on the day preceding each dose in the treatment phase [redacted] for subjects who are discharged during washout. If urine cannot be collected at the specified visit, the reason should be documented in the source document. The results of the serum pregnancy test obtained at screening must be confirmed to be negative by the investigator before receiving study drug. During the course of the study, participants will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures (not allowed within 32 days of the last dose). An additional serum or urine hCG pregnancy test will be performed at the final visit.

9.1.12.3 Contraceptive Methods for Female Participants of Childbearing Potential

- Effective contraceptive methods include the following:
  - Double-barrier method (contraceptive sponge, diaphragm, or cervical cap with spermicidal jellies or creams PLUS male condom).
  - Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action, PLUS condom with or without spermicide.

- Highly effective contraceptive methods include the following:
  - Nonhormonal Methods:
    a) IUD (intrauterine device).
    b) Bilateral tubal occlusion or bilateral tubal ligation or vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).
    c) Sexual abstinence: Sexual abstinence may be considered as a method only if defined as refraining from heterosexual intercourse and determined to be the usual lifestyle before entering the study with reliability of abstinence for the duration of the study participation and for 32 days after last dose of study drug.
- Hormonal methods:
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter until she has been on the contraceptive for 3 months.

9.1.12.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Assessment of participants compliance through such questions as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late? (Even in women with irregular or infrequent menstrual cycles, a pregnancy test must be performed if the answer is “yes.”)
  - Is there a chance you could be pregnant?

9.1.13 Pregnancy

If any participants is found to be pregnant during the study, she should be withdrawn immediately and the study drug should be immediately discontinued. In addition, any pregnancies in the partner of a male participant during the study, or for 90 days after the last dose, should also be recorded following authorization from the participant’s partner.

If the pregnancy occurs during administration of active study drug, or within 90 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the participant of their right to receive treatment information. If the participant chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Participants randomized to placebo need not be followed.

If the female participant and/or female partner of a male participant agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female participant/female partner of the participant was participating in a clinical study at the time she became pregnant and provide details of the study drug the participant received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male participants, in participants on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.14 Documentation of Screen Failure

Investigators must account for all participants with a signed informed consent. If the participant is found to be ineligible for the study before randomization, the investigator should record the primary reason for screen failure in the eCRF.

Participants may be rescreened after consultation with the medical monitor or sponsor.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Pretreatment events (PTE)/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Withdrawal by participant.
- Study terminated by sponsor.
- Other (specify reason).

9.1.15 Documentation of Entry Into the Qualification Phase

Only participants who meet all of the inclusion criteria (Section 7.1) and none of the exclusion criteria (Section 7.2) are eligible for entrance into the qualification phase.

If the participant is found to be not eligible for the qualification phase, the investigator should record the primary reason for failure on the applicable eCRF;

The primary reason for qualification failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Did not meet qualification criteria (specify reason)
- Significant protocol deviation.
- Lost to follow-up.
- Withdrawal by participant.
- Study terminated by sponsor.
- Other (specify reason).

9.1.16 Documentation of Entry Into the Treatment Phase

Participants who meet the criteria in Section 7.3 will be randomized to 1 of the 10 sequences in the treatment phase (Section 6.1).

If the participant is found to be not eligible for the treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Safety Monitoring

The sponsor's medical monitor and/or pharmacovigilance physician will monitor safety data throughout the course of the study.

9.2.1 Reporting of Abnormal Liver Function Tests

If participants experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.6 and Section 10.2.1 for the appropriate guidance participant discontinuation and on reporting AEs.)

If a participant is noted to have elevated ALT or AST >3 times the ULN on 2 consecutive occasions, the abnormality should be recorded as an SAE. In addition, eCRFs must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed. The investigator must contact the medical monitor for discussion of the relevant participant details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.1).

If a participant is noted to have ALT or AST >3 × the ULN, and total bilirubin >2 × the ULN or INR >1.5, for which an alternative etiology has not been identified, a CRF must be completed and transmitted with the SAE report form (as per Section 10.2.2). The investigator must contact the medical monitor for discussion of the relevant participant details, possible alternative etiologies,

such as acute viral hepatitis A or B, or other acute liver disease, or medical history/concurrent medical conditions, and continued participation in the study. Follow-up laboratory tests as described in Table 9.a must also be performed.

A consultation with a hepatologist may be considered as per investigator judgment or consultation with the medical monitor/sponsor.

9.2.2 Reporting of QTcF Interval Increase

If the QTcF is >500 msec or if there is an increase of QTcF >60 msec above baseline, the participant should be provided with appropriate clinical follow-up. The participant's ECG findings should be confirmed by repeat ECG with manual measurement of the QTcF interval.

The investigator must contact the medical monitor for discussion of the relevant participant details, possible alternative etiologies, such as medical history/concurrent medical conditions, and continued participation in the study.

In addition, the eCRF must be completed and transmitted with the SAE Report form (as per Section 10.2.2).

9.3 [redacted]

9.3.1 [redacted]

9.3.2 [redacted]

9.4 PD Assessments

PD measures will be administered electronically. Before completing the computerized PD measures, all participantparticipants will undergo a scripted training and practice regimen. Eligible

participants who appear to have difficulty differentiating between bipolar and unipolar VAS (eg, making errors such as selecting 50 as neutral for a unipolar scale) or difficulty distinguishing between "at this moment" and "next-day" measures during the qualification phase will undergo additional practice training on the difference between the scale types. Additional training sessions will be documented in source files.

Testing conditions for PD assessments should remain as consistent as possible across the study. Participants will be monitored carefully to ensure that they are completing the PD assessments appropriately; all reasonable attempts should be made to rouse participants who fall asleep during testing cycles.

9.4.1 Subjective Effects VASs

All VAS will be scored on a 100-point scale, as shown in Table 9.b. 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.

Table 9.b VAS Descriptions

Scale Interpretation	Include Predose	Type of Scale	Description	Question Text	Response Anchors
Balance	No	Bipolar	Drug Liking	At this moment, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking
Balance	No	Bipolar	Overall Drug Liking	Overall, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking
Balance	No	Bipolar	Take Drug Again	I would take this drug again	0: Definitely not 50: Neutral 100: Definitely so
Positive	No	Unipolar	Good Effects	At this moment, I feel good drug effects	0: Not at all 100: Extremely
Positive	Yes	Unipolar	High	At this moment, I am feeling high	0: Not at all 100: Extremely
Negative	No	Unipolar	Bad Effects	At this moment, I feel bad drug effects	0: Not at all 100: Extremely
Other	No	Unipolar	Any Effects	At this moment, I feel any drug effects	0: Not at all 100: Extremely
Other	Yes	Bipolar	Alertness/ Drowsiness	At this moment, my mental state is	0: Very drowsy 50: Neither drowsy nor alert 100: Very alert

9.4.2 [redacted]

Table 9.c [redacted]

[redacted]

9.5 Schedule of Observations and Procedures

[redacted]

9.5.1 Screening

Each participant will participate in a medical screening visit to determine eligibility. Participants will be screened within 28 days before the qualification phase. Participants will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.4 for procedures for documenting screening failures.

[redacted]

9.5.2 Qualification Phase

Within 28 days of the screening visit, eligible participants will participate in a 4-day qualification phase (from Day -1 through Day 3) to determine if participants are able to discriminate the drug effects of the positive control, alprazolam, when compared to placebo, and to demonstrate that they are able to tolerate the administered alprazolam dose.

[redacted]

9.5.3 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.

Participants eligible for the treatment phase of the study will be randomized to receive orally administered treatments (1 in each of 5 treatment periods) as shown in Section 6.1. The exact date and time of the study drug administration will be recorded in the eCRF. Participants will remain in the CRU for at least 24 hours after the last dose of the final period, then be discharged and scheduled for the follow-up procedures. After the first study treatment in the treatment phase, there will be a washout interval of at least 7 days before the subsequent study drug administration.

[redacted]

9.5.4 Follow-up (Final Visit or ET)

The final visit (can be a phone call) will be study Day 37 (7 days ±3 days following Day 1 of treatment period 5, which is the last dosing day in the study) or 7 days (±3 days) following the ET visit. [redacted]

For all participants receiving study drug, the investigator must complete the end of study eCRF page.

10.0 ADVERSE EVENTS

10.1 Definitions

In this study, AEs refers to both PTEs and TEAEs. PTEs are AEs that started before receiving any study drug. TEAEs are AEs that started after the first study drug administration.

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation participant who has signed informed consent to participate in a study but before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 TEAEs

A TEAE is defined as any untoward medical occurrence in a clinical investigation participant who has been administered a drug; it does not necessarily have to have a causal relationship with this treatment.

A TEAE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for AEs

- An untoward finding generally may:
  - Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
  - Necessitate therapeutic intervention.

  - Require an invasive diagnostic procedure.
  - Require discontinuation or a change in dose of study drug or a concomitant medication.
  - Be considered unfavorable by the investigator for any reason.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as AEs.
- Diagnoses versus signs and symptoms:
  - Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).
- Laboratory values and ECG findings:
  - Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required, or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
  - If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased serum creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.
- Pre-existing conditions:
  - Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the participant experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
  - If a participant has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").
  - If a participant has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

- Worsening of AEs:
  - If the participant experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- Changes in intensity of AEs:
  - If the participant experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.
- Preplanned procedures (surgeries or interventions):
  - Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.
- Elective surgeries or procedures:
  - Elective procedures performed where there is no change in the participant's medical condition should not be recorded as AEs but should be documented in the participant's source documents. Complications resulting from an elective surgery should be reported as AEs.
- Overdose:
  - An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study participant, at a dose above that which is assigned to that individual participant according to the study protocol. Note: Because of the double-blind nature of the study, any additional tablets or capsules ingested at a dosing event will be considered an overdose during the period in which the study is blinded. Investigator to refer to Section 8.5for decisions regarding unblinding for medical treatment.All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
  - SAEs of overdose should be reported according to the procedure outlined in Section 10.2.
  - In the event of drug overdose, the participant should be treated symptomatically.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.1.5 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the participant.
Moderate:	The event causes the participant discomfort and interrupts the participant's usual activities.
Severe:	The event causes considerable interference with the participant's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the participant and/or investigator.

10.1.9 Stop Date

The stop date of the AE is the date at which the participant recovered, the event resolved but with sequelae, or the participant died.

10.1.10 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE (eg, the study has been terminated, the participant died, dosing with study drug was already stopped before the onset of the AE).
- Dose interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/resolved – participant returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or sign/symptom has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the participant died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, sign/symptom, or laboratory value on the last day of the observed study period is worse than when it started; is an irreversible congenital anomaly; the participant died from another cause with the particular AE state remaining "not recovered/not resolved."
- Resolved with sequelae – the participant recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AE is considered as the cause of death.

- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from Visit 1. Routine collection of AEs will continue until the follow-up visit.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Participants may report AEs occurring at any other time during the study.

All participants experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until a satisfactory explanation for the changes is observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

- A sponsor SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event.

- Regardless of causality, SAEs must be reported to the sponsor Global Pharmacovigilance department or designee, to the attention of the contact listed in Section 1.1, within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible within 24 hours, then a facsimile of the completed paper-based SAE form should be sent. If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

10.3.2 Reporting of Abnormal Liver-Associated Test Results

For any participant with ALT >3 × ULN **AND** total bilirubin >2 × ULN **OR** INR >1.5 × ULN for which an alternative etiology has not been found, report the event as an SAE, contact the medical monitor and Takeda trial clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Appendix D.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each participant who signs an ICF.

The sponsor or its designee will supply study site with access to eCRFs. The sponsor will make arrangements to train appropriate study site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the study site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After submission of the eCRFs to the sponsor, any change to, modification of, or addition to the data on eCRFs should be made by the investigator with use of change and modification records of eCRFs (data clarification form) provided by the sponsor. The investigator must review the data clarification form for completeness and accuracy, and must sign and date the form.

After the lock of the study database, any change to, modification of, or addition to the data on the eCRFs should be made by the investigator with the approval from the sponsor. The investigator must review the data change for completeness and accuracy, and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the participant's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed (e)consent forms, ICFs, participant authorization forms regarding the use of personal health information (if separate from the ICFs), including consent to use digital tools and applications, if applicable, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits

from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the study site and filed with the original in the participant's chart to ensure long term legibility. Furthermore, International Council for Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before unblinding of treatment assignments. This document will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all study objectives.

13.1.1 Analysis Sets

- Qualification randomized analysis set: All participants who are randomized in the qualification phase.
- Randomized analysis set: All participants who are randomized in the treatment phase.
- 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.
- 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.
- 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.

- 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-point difference) for a participant across all treatments (including placebo)

     OR

  b) E_{max}(positive control) ≤ 55

     OR

  c) E_{max}(placebo) - E_{max}(positive control) ≥ 5.

  This analysis set will be used for PD analyses.

[redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic data will be summarized using the qualification safety analysis set and the safety analysis set. Descriptive statistics will be used to summarize data for continuous variables such as age and weight (eg, number of participants, mean, median, SD, and range) and for such categorical variables as sex, ethnicity, and race (number and percentage of participants within each category). Recreational drug/substance (alcohol, smoking) use history will also be summarized using descriptive statistics. Medical history and medication history will be listed by participant.

13.1.3 PD Analysis

13.1.3.1 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.

13.1.3.2 Primary Endpoint

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 with placebo (P)?

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

   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 (US Department of Health and Human Services, FDA, CDER: Statistical review and evaluation Application Number: 215904, Statistical Reviews, 2022).

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

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

   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 with alprazolam.

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

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

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

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.

If the variances across treatment groups shows potential heterogeneity, the model will be fitted to allow unequal variances across treatment groups. If non-normality of residuals is detected in the model, a paired t-test or sign test will be used as appropriate for hypothesis testing.

Carryover effects are defined as the effect of the treatment administered in the previous treatment period. If the carryover effect is found to be significant at a level of 0.25, then it will be included in the mixed-effects model as a fixed effect. Otherwise, carryover effect will be dropped from the model.

From the model, the least-squares mean of each difference, 1-sided 95% CIs of the difference and 1-sided p-values will be provided for each treatment comparison. The treatment difference will be estimated by the mean difference if the paired t-test is used and by the median difference if the sign test is used.

13.1.3.3 Secondary 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 hypothesis 1 and 2, and 2-sided significance level 0.10 for hypothesis 3.

1. Positive control (alprazolam) (C) versus placebo (P):

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

2. Positive control (alprazolam) (C) versus 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) versus 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.

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.

13.1.3.4 [redacted]

[redacted]

13.1.4 [redacted]

[redacted]

13.1.5 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.

All AEs will be coded using the MedDRA and characterized as pretreatment and treatment-emergent according to the intake of the study drugs. TEAEs will be summarized by treatment showing the number and percentage of participants who experienced at least 1 TEAE and the number of TEAEs reported. A by-participant AE data listing including reported term, coded term, treatment, severity, and relationship to treatment will be provided. TEAEs leading to discontinuation and SAEs will be listed separately.

Vital signs data will be summarized by study phase and treatment and will be listed by participant. Observed values and changes from baseline will be presented.

Physical examination abnormalities, ECG results, clinical laboratory values, and C-SSRS responses will be listed by participant.

13.2 Interim Analysis

No interim analysis is planned.

13.3 Determination of Sample Size

The qualification phase of the study is based on a 2 × 2 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 prematurely discontinued or are 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 hypothesis for the primary PD endpoint.

Power calculations used a paired t-test and assumed a true 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 SD of the difference between alprazolam and placebo were derived from published data (Chen and Bonson 2013; Levy-Cooperman et al. 2016; Schoedel et al. 2018a).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator guarantees access to source documents by the sponsor or its designee (contract research organization) and by the IRB.

All aspects of the study and its documentation will be participant to review by the sponsor or sponsor's designee, including but not limited to the investigator's binder, study drug, participant medical records, informed (e)consent documentation, documentation of participant authorization to use personal health information and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

In case of prolonged access restrictions to external visits (study monitors) to a study site due to COVID-19 pandemic and wherever possible by local regulations, remote source data verification (rSDV) may be considered for critical data related to participant's safety and any key variables to ensure data accuracy and integrity.

If rSDV is required, full details of the process will be included in the clinical monitoring plan following any applicable local guidance for secure access to remote source documents and data security provisions to protect personal data.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The study site should document all protocol deviations in the participant's source documents. In the event of a significant deviation, the study site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary study assessment. A protocol deviation form should be completed by the study site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be participant to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the study site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan, Center for Drug Evaluation in China). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, participants) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed (e)consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. If the study site is unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the US Department of Health and Human Services (for studies including Takeda Development Center Americas).

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the IB, the informed (e)consent form, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and participant informed (e)consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed (e)consent form) reviewed; and state the approval date. The sponsor will notify the study site once the sponsor has confirmed the adequacy of study site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study.

Study site must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed (e)consent form, recruitment materials intended for viewing by participants, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRB and sponsor.

15.2 Participant Information, Informed (e)Consent, and Participant Authorization

Written and (e)consent documents will embody the elements of informed (e)consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed (e)consent form, participant authorization form (if applicable), and participant information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies (if applicable). The informed (e)consent form and the participant information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed (e)consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed (e)consent form and if applicable, the participant authorization form. The informed (e)consent form, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB and the sponsor before use.

The informed (e)consent form, participant authorization form (if applicable), and participant information sheet (if applicable) must be written in a language fully comprehensible to the prospective participant. It is the responsibility of the investigator to explain the detailed elements of the informed (e)consent form, participant authorization form (if applicable), and participant information sheet (if applicable) to the participant. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the participant is not capable of rendering adequate informed (e)consent, then the participant's legally acceptable representative may provide such consent for the participant in accordance with applicable laws and regulations.

The participant, or the participant's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the participant, or the participant's legally acceptable representative, determines he or she will participate in the study, then the informed (e)consent form and participant authorization form (if applicable) must be signed and dated by the participant, or the participant's legally acceptable representative, at the time of consent and before the participant entering into the study. The participant or the participant's legally acceptable representative should be instructed to sign

using their legal names, not nicknames, using a ballpoint pen with either blue or black ballpoint ink in the case of written consent. The investigator must also sign and date the informed (e)consent form and participant authorization (if applicable) at the time of consent or after the receipt of participant signature (in the case of (e)consent) and before participant entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable.

Once signed, the original informed (e)consent form or certified copy (if applicable), participant authorization form (if applicable), and participant information sheet (if applicable) will be maintained by the study site. The investigator must document the date the participant signs the informed (e)consent in the participant's medical record. Copies of the signed informed (e)consent form, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be provided to the participant.

All revised informed (e)consent forms must be reviewed and signed by relevant participants or the relevant participant's legally acceptable representative in the same manner as the original informed (e)consent. The date the revised (e)consent was obtained should be recorded in the participant's medical record, and the participant should receive a copy of the revised informed (e)consent form.

15.3 Participant Confidentiality

The sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data will only be linked to the sponsor's clinical trial database or documentation via a participant identification number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age, or date of birth, and participant initials, may be used to verify the participant and accuracy of the participant's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the participant's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed (e)consent process (see Section 9.1.1).

Copies of any participant source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, participant name, address, and other identifier fields not collected on the participant's eCRF).

15.4 Clinical Trial Disclosures and Publication

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda policy/standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda policy/standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each participant in the study must be insured in accordance with the regulations applicable to the study site where the participant is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study participants. Refer to the study site agreement regarding the sponsor's policy on participant compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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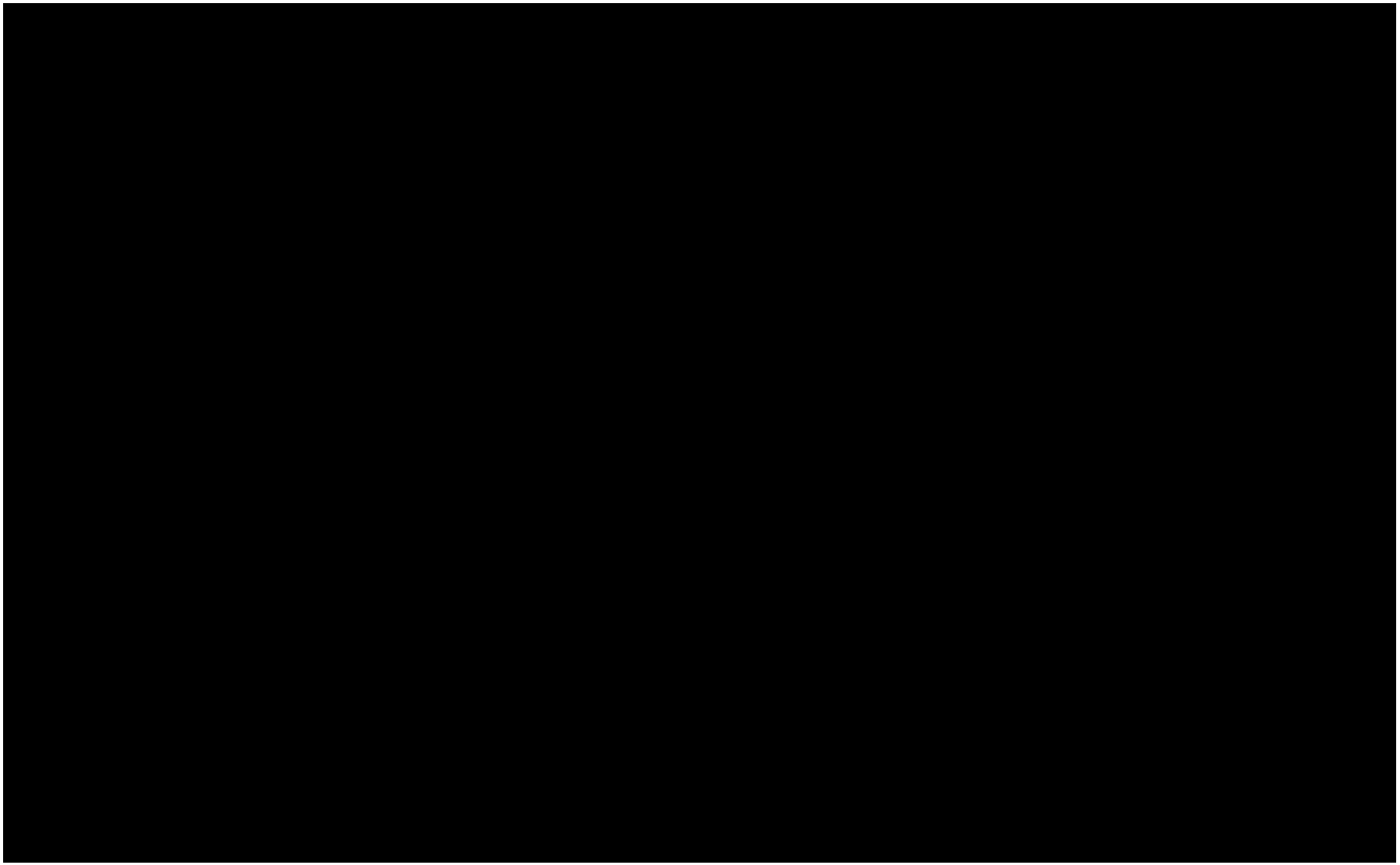
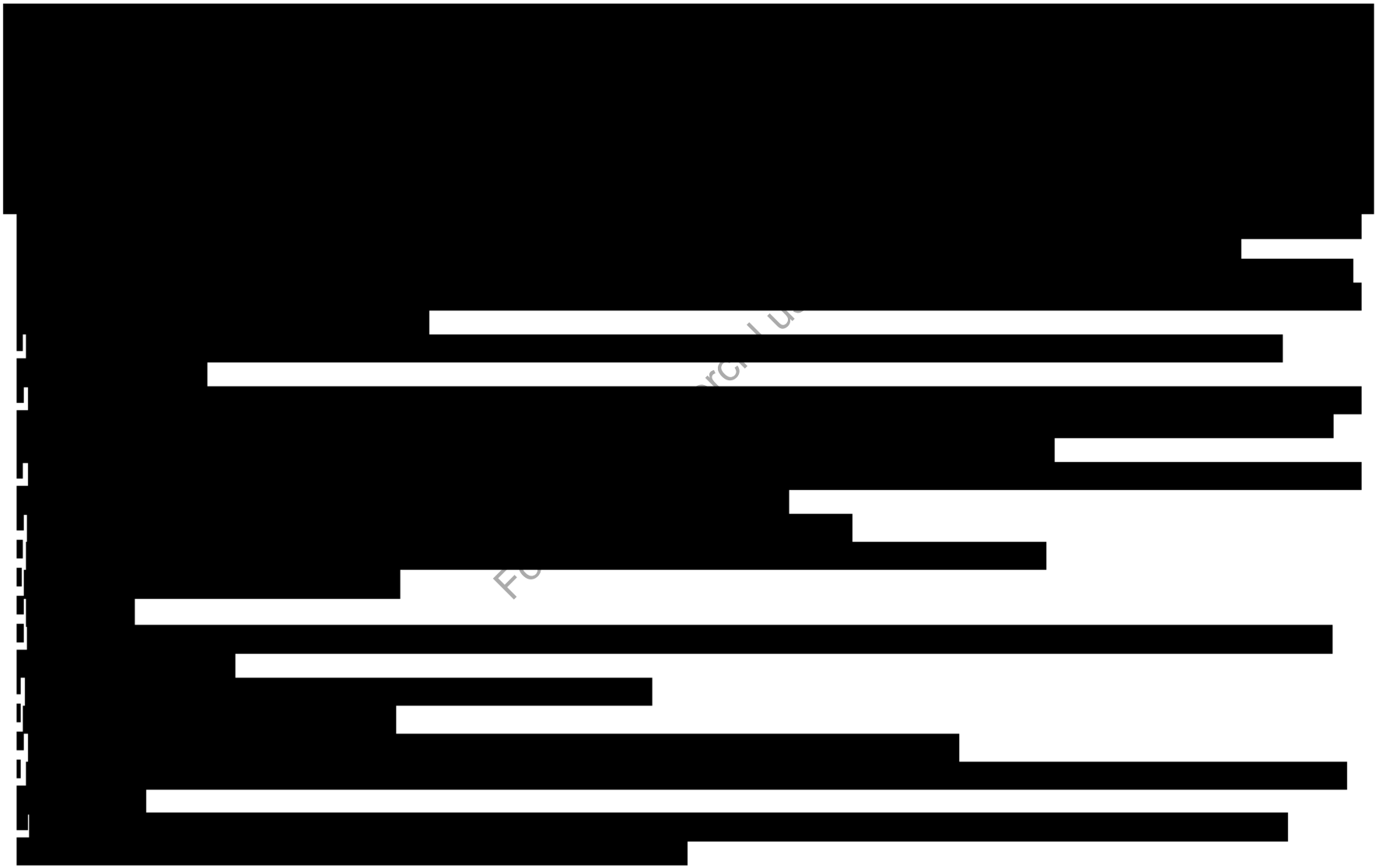
Williams, E. J. 1949. Experimental designs balanced for the estimation of residual effects of treatments. *Aust J Chem,* 2(2), 149-68.

Appendix A [redacted]

[redacted]





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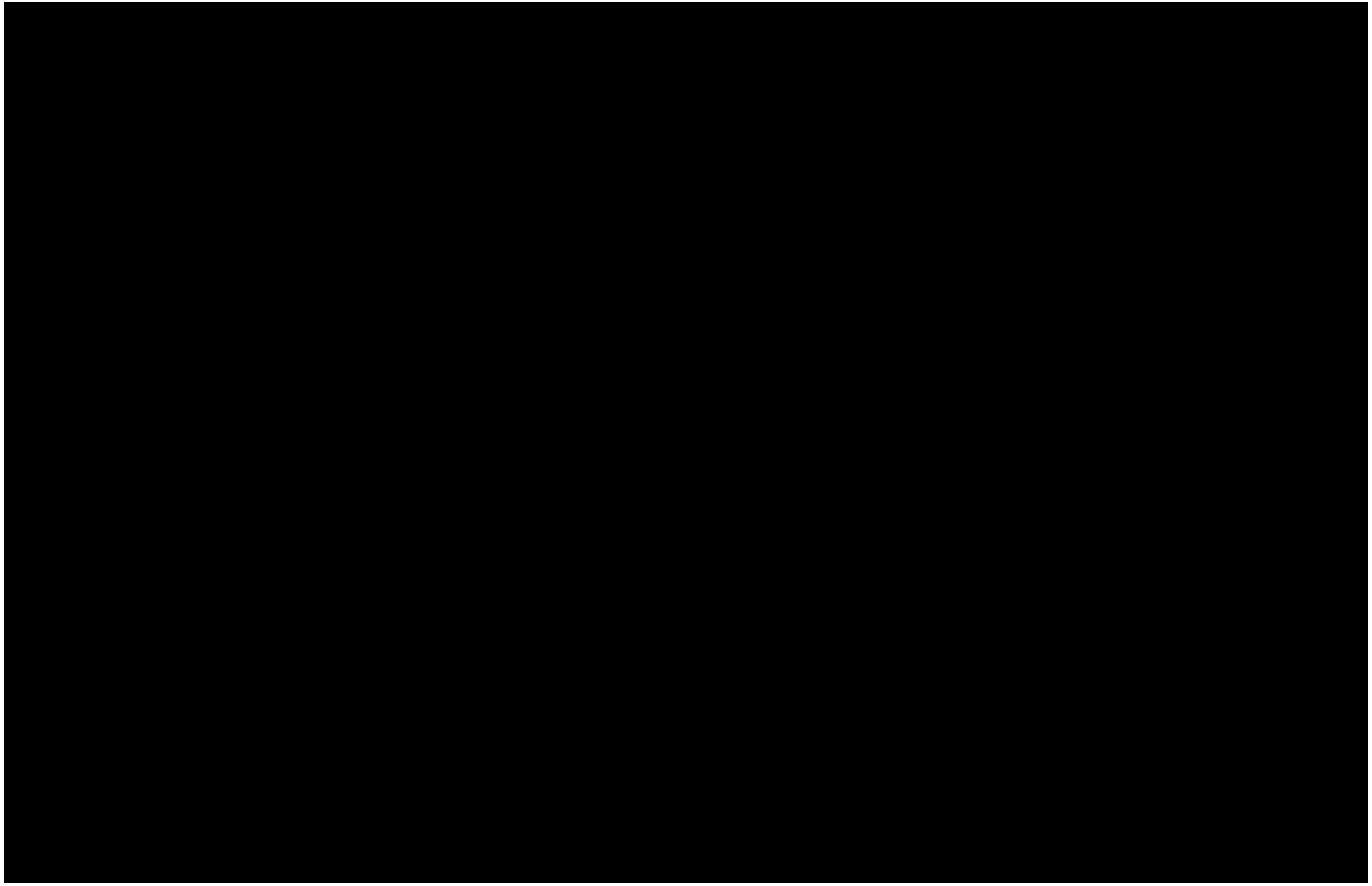

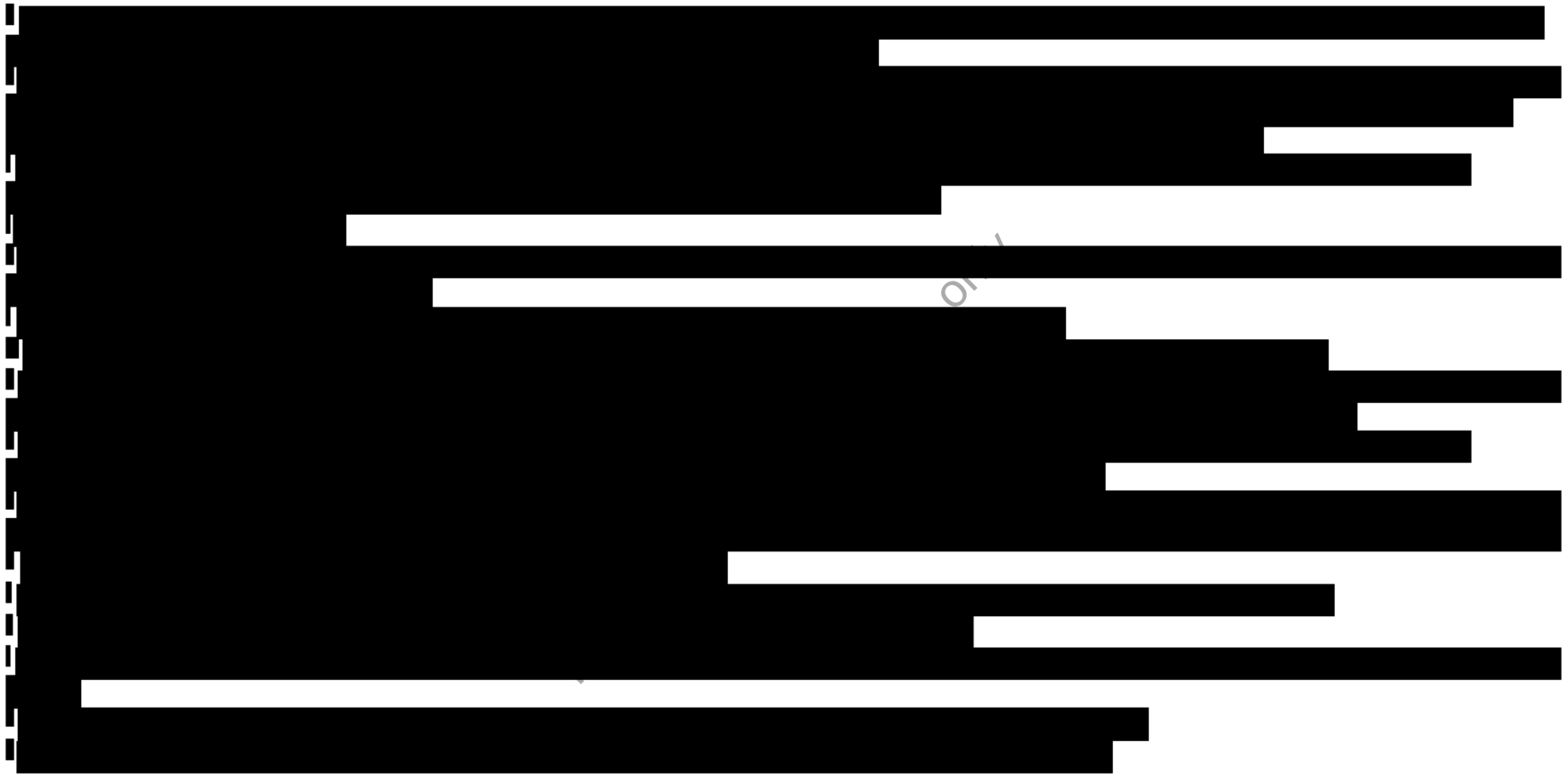

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are participant to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential participants, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed (e)consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each participant who participates in the study, and document the date of (e)consent in the participant's medical chart. Valid informed (e)consent is the most current version approved by the IRB. Each informed (e)consent form should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an informed (e)consent form does not include such a participant authorization, then the investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Participant Informed (e)Consent

In seeking informed (e)consent, the following information shall be provided to each participant:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the participant's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of participants involved in the study.
7. A description of the participant's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the participant may receive.
11. A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the participant or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the participant will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB, and the monitor may inspect the records. By signing an informed (e)consent form, the participant or the participant's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the participant for participating in the study.
17. The anticipated expenses, if any, to the participant for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), participant's rights, and IRB and whom to contact in the event of a research-related injury to the participant.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant otherwise is entitled, and that the participant or the

participant's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

20. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
21. A statement that the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the participant's participation in the study may be terminated.
24. A participant authorization (either contained within the informed (e)consent form or provided as a separate document) describing to the participant the contemplated and permissible uses and disclosures of the participant's personal information (including personal health information) for purposes of conducting the study. The participant authorization must contain the following statements regarding the uses and disclosures of the participant's personal information:

    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;

    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer participants the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

    d) that participants agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

    e) that the participant's identity will remain confidential in the event that study results are published.

25. Female participants of childbearing potential (eg, nonsterilized, premenopausal female participants) who are sexually active must use effective or highly effective contraception (as defined in the informed consent) from the time of signing informed consent throughout the duration of the study, and for 32 days following the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female participants of childbearing potential. If a participant is found to be pregnant during study, study drug will be discontinued.
26. Male partners of female participants must use effective or highly effective contraception (as defined in the informed consent) if required as part of the method (eg, double-barrier, vasectomized partner) from signing the informed consent throughout the duration of the study, and for a minimum of 32 days following the last dose of study drug.

Appendix D Trial Management During COVID-19 Pandemic

The purpose of this section is to safeguard the safety of study participants, ensure continuation of study conduct and uninterrupted maintenance of treatment, and preserve the integrity of the study, in case of a general public health crisis or pandemic, such as COVID-19. This section addresses situations in which scheduled in-person clinic visits are not feasible due to local, regional or national restrictions.

The principal investigator holds the ultimate responsibility for the safety and well-being of study participants and shall maintain compliance with the current local and health authority guidelines and recommendations pertaining to the pandemic. The study procedures outlined in this protocol may be modified subsequently according to any emerging or revised health authority guidelines during conduct of the trial due to the ongoing COVID-19 pandemic. These modified study procedures are to be used only during the COVID-19 pandemic.

Due to the COVID-19 pandemic, study participants may not be able to attend scheduled in-person clinic visits as per protocol. The study site should follow local and country health and government authorities' restrictions and recommendations on conduct of clinical trials during the pandemic.

COVID-19 vaccination of participants is allowed during the study.

Any protocol deviations, missing visits, or missing assessments related to COVID-19 restrictions will be recorded and reported in the CSR.

Amendment 1 to 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	16-Mar-2023 13:59 UTC
[redacted]	Biostatistics Approval	16-Mar-2023 17:09 UTC
[redacted]	Clinical Science Approval	16-Mar-2023 20:02 UTC
[redacted]	[redacted] Approval	20-Mar-2023 15:27 UTC