Adaptive Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of Kratom in Healthy, Nondependent, Adult Recreational Polydrug Users with Opioid Experience

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STATISTICAL ANALYSIS PLAN

For:

Food and Drug Administration (FDA), USA

PROTOCOL No. 75F40121C00199

ADAPTIVE STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE ASCENDING DOSES OF KRATOM IN HEALTHY, NONDEPENDENT, ADULT RECREATIONAL POLYDRUG USERS WITH OPIOID EXPERIENCE

Altasciences Project No. FDU-P4-117

Prepared by:

Altasciences Company Inc.

575 Armand-Frappier Boulevard

Laval, Quebec

Canada, H7V 4B3

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STATISTICAL ANALYSIS PLAN AND SHELLS APPROVAL

We have carefully read this statistical analysis plan and corresponding shells and agree it contains the necessary information required to handle the statistical analysis of study data.

Anita Shanker Senior Biostatistician Altasciences Company, Inc.	Date
Christopher Intehar, B.Sc. Pharmacology Associate I Altasciences Company, Inc.	Date
Lisa Hickey Senior Director, Statistics Inference, Inc.	Date

On behalf of the Sponsor:

Chad J. Reissig, Ph.D. Supervisory Pharmacologist Center for Drug Evaluation and Research Office of the Center Director, Controlled Substance Staff U.S. Food and Drug Administration	Date

VERSION CONTROL

Version	Date	Author	Description of Changes
1.0	2024/01/04	Anita Shanker/ Christopher Intehar/ Lisa Hickey	Not applicable

SUMMARY OF CHANGES

Description	Section/Location	Rationale

TABLE OF CONTENTS

TABLE OF TABLES

ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis Of Variance
ARCI	Addiction Research Center Inventory
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
DMP	Data Management Plan
DTS	Deviation Tracking System
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
LLOQ	Lower Limit Of Quantitation
ln	Natural Logarithm
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Max	Maximum
NCA	Non-Compartmental Analysis
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, and Listings
VAS	Visual Analog Scale

WHODrug World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented for the analyses of data from the Clinical Study Protocol 75F40121C00199. The analyses described in the SAP are based upon the final version of the Clinical Study Protocol 1.0, dated 2023/06/05.

2 STUDY OBJECTIVES

The objectives of the study and corresponding study endpoints are detailed in Table 2-1.

Table 2-1 Objectives and Related Endpoints

Objective	Endpoint
Primary	
The primary objective of the study is to evaluate the safety and tolerability of single ascending oral doses of kratom relative to placebo when administered in healthy nondependent recreational polydrug users with opioid experience.	Safety will be evaluated through the assessment of adverse events (AEs), laboratory tests, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), electrocardiogram (ECG), physical examination findings, and Columbia Suicide Severity Rating Scale (C-SSRS).
Secondary	
To evaluate the pharmacokinetics (PK) ofmitragynine,7-hydroxy-mitragynine,paynantheine, speciogynine, and speciociliatine following single ascending oral doses of kratom in healthy nondependent recreational polydrug users with opioid experience.	The PK endpoints of this study are the following PK parameters of mitragynine, 7 hydroxymitragynine, paynantheine, speciogynine, and peciociliatine: Maximum observed concentration (C_{max}), time of maximum observed concentration (T_{max}), area under the concentration-time curve from time zero to the last observed concentration (AUC_{0-T}), and area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$). Additionally, dose-normalized PK parameters (C_{max}/D, AUC_{0-T}/D, and $AUC_{0-\infty}/D$) will be estimated.

To evaluate the pharmacodynamics (PD) of single ascending oral doses of kratom in healthy nondependent recreational polydrug users with opioid experience.	The PD endpoint of this study is the maximum (peak) effect (E_{max}) over 24 hours for Drug Liking ("at this moment"), assessed on a bipolar (0 to 100 points) visual analog scale (VAS). Key secondary PD endpoints are: • Overall Drug Liking VAS (E_{max}) • Take Drug Again VAS (E_{max}) • High VAS (E_{max}) Non-key secondary PD endpoints are: • Balance of Effects o Drug Liking VAS (minimum effect [E_{min}], time of maximum effect [TE_{max}], time of minimum effect [TE_{min}], and time-averaged area under the effect-time curve [TA_AUE]) • Positive Effects o Good Effects VAS (E_{max}, TE_{max}, and TA_AUE) o High VAS (E_{max}, TE_{max}, and TA_AUE) • Negative Effects o Bad Effects VAS (E_{max}, TE_{max}, and TA_AUE) • Other Subjective Effects o Any Effects VAS (E_{max}, TE_{max}, and TA_AUE) o Feeling Drunk VAS (E_{max}, TE_{max}, and TA_AUE) o Drowsiness/Alertness VAS (E_{max}, TE_{max}, E_{min}, TE_{min}, and area over and under the effect-time curve [TA_AOE, TA_AUE]) o Relaxation/Agitation (E_{max}, TE_{max}, E_{min}, TE_{min}, and TA_AOE, TA_AUE) o ARCI MBG Scale (E_{max}, TE_{max}, and TA_AUE) o ARCI A Scale (E_{max}, TE_{max}, and TA_AUE) o ARCI BG Scale (E_{max}, TE_{max}, and TA_AUE) o ARCI PCAG Scale (E_{max}, TE_{max}, and TA_AUE)

	○ ARCI LSD Scale (E_{max}, TE_{max}, and TA_AUE) ○ Bowdle VAS Internal and External Perceptions composite scores (E_{max}) ○ Drug Similarity VAS12-hour postdose scores • Pupillometry ○ Maximum pupil constriction as assessed by the difference between initial pupil diameter and MPC ○ Time to maximum pupil constriction ○ Pupillometry area over the curve (time--averaged pupillometry area over the effect curve relative to baseline [TA_PAOC])

3 STUDY DESIGN

3.1 General Description

This single center, single-dose, randomized, adaptive, double-blind, placebo--controlled study will consist of 5 SAD cohorts. A total of 40 healthy, male and female nondependent, recreational polydrug users with opioid experience (8 subjects in each of the 5 cohorts) will be included.

Subjects will only participate in 1 cohort. The planned dose levels by cohort are presented in Table 3-1.

Table 3-1 Sample Dose Levels

Cohort	Number of Subjects (active:placebo)	Dose[a]	Regimen
1	8 (6:2)	1 g (2 capsules)	Single oral administration of kratom or placebo on Day 1
2	8 (6:2)	e.g., 2 g (4 capsules)	
3	8 (6:2)	e.g., 4 g (8 capsules)	
4	8 (6:2)	e.g., 6 g (12 capsules)	
5	8 (6:2)	e.g., 8 g (16 capsules)	

a. Or until the maximum tolerated dose is defined

Dose levels presented are approximations and may be increased or decreased based on interim safety reviews. Doses may be increased, above those shown above in Table 3-1, if there are no safety concerns and if it is deemed that there are minimal effects on PD measures. The upper dose may exceed 8 g if deemed appropriate and safe by interim data reviews.

Subjects will be confined to the clinical site from the day prior to drug administration until 48 hours following drug administration. Subjects will return to the clinical site for a Follow-Up Visit on Day 7 ± 2. The total duration of the study including Screening will be up to 37 days.

Blood samples for PK assessments will be collected before and over 48 hours after study drug administration. Assessments for the evaluation of PD will be performed before and over 24 hours after study drug administration. Safety and tolerability will be assessed throughout the study.

Following completion of each cohort, a Safety Review Committee (SRC) will review all safety and/or PD data to evaluate progression to the next dose cohort. The SRC will be comprised of the Principal Investigator at the Investigational site, the Study Manager and personnel from the Sponsor's scientific team at a minimum. Dosing of each cohort will be adequately scheduled apart to ensure sufficient time for review of the safety and PD data prior to dosing of the next cohort.

Subjects who terminate the study early will perform End of Study procedures (procedures from the Follow-Up Visit) as soon as possible after the time of Early Termination.

3.2 Treatments

The following treatments will be administered in this study:

3.2.1 Kratom 500 mg Capsules

Kratom capsules consist of 500 mg kratom leaf powder filled into light blue gelatin capsules. Kratom 500 mg capsules are manufactured by Sun Distribution, Super Organics for oral administration.

3.2.2 Placebo

Placebo capsules made with microcrystalline cellulose will be matched to Kratom 500 mg Capsules. The weight will be matched to the Kratom 500 mg Capsules and the composition will be the same, including excipients.

3.3 Study Procedures

For complete details on the study assessments to be performed for each study period, refer to APPENDIX A.

3.4 Randomization and Unblinding Procedures

In each cohort, subjects will be randomized 6:2 (active: placebo). The clinical site will generate the randomization code with a computer program according to the study design, the number of subjects and the number of treatments. Once generated, the randomization code will be final and will not be modified.

The randomization code will not be available to the personnel of the bioanalytical facility until the bioanalytical phase of the study has been completed. The treatment assignment (active or placebo) will not be known by the study participants. Study participants will be informed of the dose range they could receive but will not be informed of the actual dose assigned to them.

Furthermore, the randomization code will not be available to the Investigator and clinical staff involved in the collection, monitoring, revision, or evaluation of AEs, as well as clinical staff who could have an impact on the outcome of the study including the pharmacokineticist (or

delegate) and biostatistician, until all the CRFs have been approved and signed and the bioanalytical phase of the study has been completed.

The preparation and/or administration of the products will be done by designated personnel who are not directly involved in the clinical aspects of the trial.

The randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by an Investigator for further treatment to the subject or to complete a SAE report. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be recorded.

The results of the PD analyses will be made available only to the personnel responsible for evaluating the safety data before proceeding with the next dose level.

3.5 Determination of Sample Size

No formal sample size analysis was performed. It is estimated that 8 subjects per cohort with 6 subjects assigned to the active drug and 2 subjects assigned to the placebo should be sufficient to meet the objectives of the study.

4 ANALYSIS POPULATIONS

4.1 Randomized Population

The Randomized population will include all subjects who are randomized to receive either active drug (kratom) or placebo in each cohort.

4.2 Safety Population

The Safety population will include all subjects who received 1 dose of the active drug (kratom) or placebo.

4.3 Pharmacokinetic Population

The PK population will include all subjects who have received at least 1 dose of the investigational product (IP) and have at least 1 mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, or speciociliatine postdose evaluable PK sample collected (based on viable PK samples).

Subjects who do not complete the blood sampling schedule may be included in the PK population for only the PK parameters that are judged not to be affected by the missing sample(s).

Subjects with protocol deviations or adverse events that could be considered to have an impact on the PK results may be excluded from the PK population. Participants who received only placebo will not be included in the PK population.

4.4 Completer Population

All subjects in the Safety population who complete the dose level or placebo in their cohort, and have sufficient data for evaluation of the primary endpoint (based on a blinded review of data prior to database lock) will be included in the Completer population. Subjects who do not have at least 1 observation within 2 hours of T_{max} for Drug Liking VAS will be excluded from the Completer population.

5 DATA HANDLING AND PRESENTATION

All safety and statistical outputs will be generated using SAS software, version 9.4 or higher. The PK outputs will be generated using the same version of SAS.

All programs used to generate statistical analyses will be validated according to Altasciences' Standard Operating Procedures (SOPs).

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock and/or prior to breaking the blind. Any analyses performed subsequent to database lock and/or breaking the blind will be considered post hoc and exploratory, and will be identified in the Clinical Study Report (CSR).

5.1 Safety Analysis Presentation

Adverse events and medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology as defined in the study Data Management Plan (DMP).

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary (WHODrug) as defined in the study DMP.

In general, all safety summary tables will be presented for the safety population. Summaries for AEs will be presented by treatment (active dose levels and pooled placebo) and overall. Summaries for other safety endpoints will be presented by treatment (active dose levels and pooled placebo).

In general, the data listings will include all subjects in the safety population up to the point of study completion or discontinuation; exceptions will be listings pertaining to a subset of subjects only (e.g., subjects with protocol deviations) or a subset of records/events (e.g., abnormal laboratory values). Limited data for those not included in the safety population, e.g., who failed screening, may be presented, as appropriate.

Categorical variables will be summarized using sample size (N), number of available data (n), and the percentage of available data (%) for each class. Continuous variables will be summarized using descriptive statistics, including N, n, arithmetic mean (mean), standard deviation (SD), minimum (min), median, and maximum (max).

The following general considerations may be applied:

- Study Day will be derived from the reference date (e.g., the day of the first dose of study drug) and date of event as:

  Study Day = (date of event – reference date) +1, if event is on or after the reference date;

  Study Day = date of event – reference date, if event is before the reference date.

- Duration will be calculated using the general formula: (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value may be appropriately determined and used in the statistical analyses. In general, a value below the lower limit of normal range such as '<10' or '≤5' will be treated as half of the lower limit, '5' or '2.5', respectively, and a value above the upper

limit of normal range such as '>100' will be replaced with a number deemed scientifically reasonable, e.g., 101. However, the actual values as reported in the database will be presented in data listings.

- Unscheduled assessments will not be included in descriptive summary, except for baseline consideration. When assessments are repeated for a given timepoint or performed at unscheduled times, only the result which is the closest to the dosing time will be included in summary tables.

In general, summary statistics for raw variables (i.e., variables measured at the study site or central laboratory) will be displayed as follows:

- Minima and maxima will be displayed to the same number of decimal places as the raw data
- Means, medians, and quartiles (if presented) will be displayed to 1 additional decimal place
- Standard deviations will be displayed to 2 additional decimal places
- Percentages will be displayed to 1 decimal place; Percentages between 0 and 0.1 (exclusive) will be displayed as '<0.1'
- P-values will be displayed to 3 decimal places; P-values that are less than 0.001 will be displayed as '<0.001'

Derived variables (i.e., variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be displayed with the same precision as the raw data, as appropriated, then follow the similar rules in presentation of summary statistics.

5.2 Pharmacokinetic Analysis

The PK analysis will be carried out according to Altasciences SOPs.

In general, all PK summary tables will be presented for the PK population.

Individual raw PK concentrations will be displayed with the same precision as received from the bioanalytical laboratory.

Precision for individual PK parameters will be displayed as follows:

- Concentration-derived parameters (e.g., C_{max} and AUCs) will be displayed with the same precision as the raw PK concentration data.
- Parameters associated with time (eg, time of maximum concentration [T_{max}] and terminal elimination half-life [T_{half}]) will be displayed with 2 decimal places.
- Percentages will be displayed with 2 decimal places.
- Coefficient of determination (R^2) and elimination rate constant (λ_Z) will be displayed with 4 decimal places.

Summary statistics for concentration and PK parameters will be displayed with the same precision as the individual values, with the exception of number of observations (N) and CV% which will be presented with 0 and 1 decimal place, respectively.

5.3 Baseline

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first dose of study drug, including unscheduled assessment(s), if applicable.

5.4 Methods for Handling Missing Data

In general, no imputations of values for missing safety data (i.e., blank, “Not Done”, “Not Applicable”, etc.) will be performed and data presentations will reflect the data point as it appears in the Case Report Form (CRF) or electronic data file.

The handling of missing PK data is detailed in SAP Section 8.1.

6 STUDY SUBJECTS

Unless otherwise specified, all available data will be listed and summary table for disposition will be presented for the safety population.

6.1 Disposition

Subject disposition will be summarized by treatment (active dose levels and pooled placebo) and overall, including:

- Number of subjects randomized
- Number of subjects who received study drug
- Number (%) of subjects who completed the study
- Number (%) of subjects discontinued from the study overall and by primary reason for discontinuation
- Number (%) of subjects included in each of the analysis populations

The percentages will be calculated using the number of subjects who received study drug.

Listings of subject’s disposition and subjects included in each of the analysis populations will be provided.

6.2 Protocol Deviations

Deviations will be collected in the clinic deviation tracking system (DTS) and presented in a general protocol deviation listing.

7 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Unless otherwise specified, all available data will be listed and summary tables for demographics and other baseline characteristics will be presented for the safety, PK and completer populations.

The following will be presented in listings:

- Medical history
- Prior and concomitant medications
- Female and male contraceptive quesionnaires
- Substance use habits (Recreational Drug, Alcohol, Caffeine, Nicotine)

8 PHARMACOKINETIC ANALYSIS

The PK analysis will be carried out according to Altasciences SOPs. Unless otherwise specified, all available PK data and analysis results will be presented for the PK Population.

8.1 Missing Values

The lack of concentration values due to failure to collect the sample, a lost or compromised sample or due to the subject's early termination from the study will be termed "missing" in the dataset, and no imputation will be done.

If the actual collection time of a postdose PK sample is unknown, but a valid concentration value has been measured, the sample will be set to missing in the PK analysis and will be presented in listing excluded from descriptive statistics.

8.2 Measurements Below the Lower Limit of Quantitation

Concentration values below the lower limit of quantitation (LLOQ) associated with predose and postdose collection times will be replaced with zero for the non-compartmental analysis (NCA).

Concentration values below the LLOQ will be replaced with zero for mean PK profile representations as well as for descriptive statistic calculations.

Concentration values below the LLOQ that are embedded between two quantifiable concentrations will be replaced with missing for the NCA, mean PK profile representation as well as for descriptive statistic calculations.

8.3 Actual Time

The NCA will be based on actual sampling times, except for predose samples, which will be reported as zero, regardless of time deviations.

The individual plasma concentration-time profiles will be presented using actual sampling times whereas the mean plasma concentration-time profiles and tables presenting summary statistics of concentration-time series will be presented using nominal sampling times.

Actual times for plasma PK sample collections will be listed in the report.

8.4 Non-Compartmental Analysis

The following configuration for the NCA analysis (with Phoenix® WinNonlin® version 8.0, or higher) will be used:

- Data: Serial Sampled Data
- Model/Dose options Type: Plasma (200 -202) / Extravascular
- AUC Calculation Method: Linear-Up/Log-Down
- Lambda Z (λ_Z) calculation: Best fit method for λ_Z Linear-Log regression

Reasons for excluding PK parameters will include the following:

- AUC: AUC parameters will not be estimated if less than 3 consecutive measurable concentrations are observed
- PK parameters requiring λ_Z estimation (eg, $AUC_{0-\infty}$ and T_{half}) will be set to Not Reported (NR) in the tables and listings if they meet one of the following:
  - $R^2 < 0.8$
  - The terminal half-life is higher than 2 times the time interval over which λ_Z is estimated (ie. T_{half} > twice the time interval difference between $\lambda_{Z\ Upper}$ and $\lambda_{Z\ Lower}$).

The PK parameters for mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and speciociliatine are defined in Table 8-1.

Table 8-1 Pharmacokinetic Parameters of Mitragynine, 7-Hydroxy-Mitragynine, Paynantheine, Speciogynine, and Speciociliatine in Plasma

Parameter	Definition
C_{max}	Maximum observed concentration
C_{max}/D	Dose-normalized C_{max} calculated at C_{max} / Dose
T_{max}	Time of maximum observed concentration; if it occurs at more than 1 timepoint, T_{max} is defined as the first timepoint with this value
AUC_{0-T}	Area under the concentration time curve from time zero to the time of last quantifiable concentration (T_{last})
AUC_{0-T}/D	Dose-normalized AUC_{0-T} calculated as AUC_{0-T} / Dose
$AUC_{0-\infty}$	Area under the concentration time curve extrapolated to infinity, calculated as $AUC_{0-T} + C_{last}/\lambda_Z$, where C_{last} is the last quantifiable concentration at time T_{last}
$AUC_{0-\infty}/D$	Dose-normalized $AUC_{0-\infty}$ calculated as $AUC_{0-\infty}$ / Dose
AUC%Extrap	Extrapolated area (ie, percentage of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity: $AUC_{0-\infty} - AUC_{0-T}/ AUC_{0-\infty}*100$)
λ_Z	Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve
T_{half}	Terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$
The following PK parameters will be used for PK calculation and presented in the PK listings only	
T_{last}	Time of last measurable observed concentration
C_{last}	Observed concentration corresponding to T_{last}
$\lambda_{Z\ Upper}$	Upper limit on time for values included in the calculation of λ_Z
$\lambda_{Z\ Lower}$	Lower limit on time for values included in the calculation of λ_Z
Number of Points	Number of data points in computing λ_Z

Parameter	Definition
R^2	Goodness of fit for the terminal phase

8.5 Pharmacokinetic Statistical Methodology

All tables, figures, and listings (TFLs), when appropriate, will be stratified by cohort.

8.5.1 Summary Statistics

Summary statistics of the individual concentration data and derived parameters will be calculated with SAS for the PK population. Summary statistics will be calculated for concentration at each individual time point and for all PK parameters.

Concentration data will be listed by subject number and summarized by treatment using the following statistics: number of observations (N), mean, SD, min, median, max, and coefficient of variation (CV%). The PK parameters will be summarized using these same statistics, as well as geometric mean and geometric CV%.

8.5.2 Statistical Analysis

Natural log-transformed PK parameters (C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}T}$) will be assessed statistically for proportionality. Proportionality analysis will be done using a power model. The power model is defined as:

$$\ln(\text{PK parameter}) = \alpha + \beta \bullet \ln(\text{Dose}) + \varepsilon$$

where α is the intercept, β is the slope and ε is the error term. A linear model with ln-transformed dose as a continuous effect will be fitted. A point estimate and a 90% confidence interval will be derived for the slope (β).

The mixed effect statistical model using PROC MIXED procedure in SAS will be used for dose proportionality assessment. If the mixed model failed to converge, a PROC GLM will be used. If there are less than 3 subjects for valid PK parameters (C_{max}, $AUC_{0\text{-}T}$ and $AUC_{0\text{-}\infty}$) or less than 3 subjects for one of valid PK parameters per cohort, this cohort or particular PK parameter within this cohort would be considered as exclusion of dose proportionality assessment.

The parameter can be considered to be dose-proportional if the 90% CIs for the slope coefficient that include 1 will suggest evidence of dose proportionality.

Dose proportionality may be assessed within different dose ranges if deemed appropriate with at least three doses.

9 PHARMACODYNAMIC ANALYSIS

Unless otherwise specified, all available PD data and analysis results will be presented for the Completer population.

The PD measures at each time point will be summarized by treatment using descriptive statistics and presented graphically. Derived endpoints will be summarized by treatment and paired difference using descriptive statistics.

Descriptive statistics will include n, mean, standard error (SE), minimum, first quartile (Ql), median, third quartile (Q3) and maximum for all PD values and endpoints other than TE_{max} and TE_{min}. For TE_{max} and TE_{min}, minimum, Q1, median, Q3 and maximum will be presented.

Derivations for PD endpoints will be calculated as described below:

PD Endpoints	Definition
E_{min}	Minimum observed post-dose effect
E_{max}	Maximum observed post-dose effect
TE_{min}	Time of minimum observed post-dose effect
TE_{max}	Time of maximum observed post-dose effect
TA_AUE[1]	Time-averaged area under the effect-time curve (pre-dose - post-dose)
TA_AOE [1]	Time-averaged area over the effect-time curve (pre-dose - post-dose)

[1] For time-averaged area over the effect-time-curve and area under the effect-time-curve (TA-AUE and TA_AOE), will be calculated as the area over(or under) the curve relative to the baseline value divided by the time from time 0 to the X hour time point. TA_AOE will be calculated using the linear trapezoidal rule applied to non-missing data. TA_AOE will not be calculated if the first or last scheduled time point are missing. Assessments performed outside the assessment windows may be excluded from by-time point summary statistics; this will be determined prior to unblinding.

Derived Variable	Variables Used	Calculation	Comment
TA_AUE and TA_AOE	PD effect score E_i at actual elapsed times t_i over one inter-dosing interval.	$AUE_i = (t_i - t_{i-1})\frac{(E_i + E_{i-1})}{2}$ then $AUE = \sum_{i=1}^{n} AUE_i$, summation over all time intervals from time 0 (or the first time point if the PD measure is not collected predose) to the X-hour (ie, last) time point. TA_AUE is calculated as the AUE divided by the time from time 0 (or the first time point if the PD measure is not collected predose) to the X-hour time point. TA_AOE will be calculated using the same procedure and TA_AUE with the exception that increases compared to baseline are expected so areas are expected to fall over basline instead if below baseline.	Trapezoidal rule used to the 2 consecutive non-missing data points Missing data are ignored. The actual elapsed time t_0 for the predose value is set to 0.

9.1 Pupillometry

Pupillometry will be used as an objective physiological PD measure as it is a sensitive measure of central opioid action and appears to be resistant to tolerance development with repeated administration. An electronic pupillometer will be used to measure pupil diameter. For each subject, every effort will be made to use the same eye for all assessments throughout the study. The pupillometry assessments will be completed immediately prior to the administration of all other PD measures. Pupil diameter will be measured as per the timepoints outlined in Table 9-1.

Table 9-1. Pupillometry Schedule

Pupillometry - Scheduled Time Points
Day 1: predose and 0.5 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours postdose Day 2: 24 hours postdose

Windows for timed pupillometry measurements are presented in Table 9-2.

Table 9-2. Acceptable Windows for Timed Pupillometry Measurements

Elapsed Time	**Accepted Window**
Predose (Day 1)	Within 60 minutes prior to study drug administration
Postdose	Within 5 minutes following collection of PK blood sample

The following Pupillometry endpoints will be derived.

- Maximum pupil constriction as assessed by the difference between initial pupil diameter and minimum pupil diameter (MPC)
- Time to maximum pupil constriction
- Pupillometry area over the curve (time-averaged pupillometry area over the effect curve relative to baseline [TA_PAOC]). TA_PAOC will be calculated as the area over the effect curve relative to baseline divided by the time from time 0 to the last time point post-dose or specific time point.

Pupil diameter will be summarized by treatment, visit and time point using descriptive statistics. Derived endpoints will also be summarized by treatment using descriptive statistics.

9.2 Subjective Effects

Subjective measures are detailed in Table 9-3.

Table 9-3. Subjective Measures Schedule

Category	Evaluations	Timepoints
Drug-specific VAS	Drug Liking, Good Drug Effects, Bad Drug Effects, and Any Drug Effects	0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose
	Overall Drug Liking and Take Drug Again	12 and 24 hours postdose
Other VAS	High, Feeling Drunk, Relaxation/Agitation, Drowsiness/Alertness, and Bowdle VAS	Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose
	Drug Similarity	12 hour postdose
ARCI Scales	MBG, A, BG, PCAG, and LSD	Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose

Abbreviations: A = amphetamine; BG = Benzedrine Group; LSD = Lysergic Acid Diethylamide; MBG = Morphine-Benzedrine Group; PCAG = Pentobarbital–Chlorpromazine–Alcohol Group; VAS = visual analog scale.

Windows for timed subjective measurements are presented in Table 9-4.

Table 9-4. Acceptable Windows for Timed Subjective Measurements

Elapsed Time	Accepted Window
Predose (Day 1)	Within 60 minutes prior to study drug administration
Postdose	Within 5 minutes following pupillometry assessment

9.2.1 Visual Analogue Scales

All VAS will be scored on a 100-point scale, as shown in Table 9-5, and will be administered at the timepoints specified in Table 9-3. 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. Bipolar scales ask about the neutrality, the direction and the intensity of a subjective opinion, whereas unipolar scales only ask about the extremity or intensity of a subjective opinion. When VAS are administered as bipolar scales, a neutral point equal to 50 is embedded within the scale (e.g., Drug Liking, Overall Drug Liking, Take Drug Again, Drowsiness/Alertness VAS). The neutral point reflects a state whereby a subject is experiencing neither negative nor positive effects (e.g., neither dislike nor like the effects of the drug) and is

labeled with an anchor, such as “neither like nor dislike.” When VAS are administered as unipolar scales, anchors will be presented using text such as “Not at all” (score = 0) to “Extremely” (score = 100; e.g., Good, Bad, High, and Any Effects VAS). Unipolar scales do not include a neutral point but rather, a rating of “0” reflects the complete absence of a subjective effect while a rating of “100” reflects the maximum presence of a subjective effect (e.g., No Good Effects = 0, Extremely Good Effects = 100). Scales that refer specifically to drug (e.g., Drug Liking, Good Effects VAS, Bad Effects VAS, and Any Effects VAS) are not administered at predose.

Table 9-5. Visual Analog Scale (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	
Balance	No	Bipolar	Take Drug Again	I would take this drug again	0: Definitely would not 50: Neither would nor would not 100: Definitely would
Positive	Yes	Unipolar	High	At this moment, I am feeling high	0: Not at all 100: Extremely
Positive	No	Unipolar	Good Effects	At this moment, I feel good drug effects	
Negative	No	Unipolar	Bad Effects	At this moment, I feel bad drug effects	
Other	No	Unipolar	Any Effects	At this moment, I feel any drug effect	
Other	Yes	Unipolar	Feeling Drunk	At this moment, I am feeling drunk	

Scale Interpretation	Include Predose	Type of Scale	Description	Question Text	Response Anchors
Other	Yes	Bipolar	Drowsiness/Alertness	At this moment, my mental state is	0: Very drowsy 50: Neither drowsy nor alert 100: Very alert
Other	Yes	Bipolar	Relaxation/Agitation	At this moment, my mental state is	0: Very relaxed 50: Neither relaxed nor agitated 100: Very agitated

9.2.2 Bowdle VAS

The Bowdle VAS consists of 13 items for which the subject is asked to rate his or her current feelings. An adapted computerized version of Bowdle VAS will be administered. The first 11 items are used to derive two composite scores reflecting internal and external perceptions. Each VAS will be administered using a unipolar format and scored from 0 to 100, with 0 reflecting "Not at all" and 100 reflecting "Extremely." Lower individual and overall scores indicate fewer psychedelic effects.

The individual items of the questionnaire are listed below:

1. My body or body parts seemed to change their shape or position (BODY)
2. My surroundings seemed to change in size, depth, or shape (SURROUNDINGS)
3. The passing of time was altered (TIME)
4. I had feelings of unreality (REALITY)
5. It was difficult to control my thoughts (THOUGHTS)
6. The intensity of colors changed (COLORS)
7. The intensity of sound changed (SOUND)
8. I heard voices or sounds that were not real (VOICES)
9. I had the idea that events, objects, or other people had particular meaning that was specific for me (MEANING)
10. I had suspicious ideas or the belief that others were against me (SUSPICIOUS)
11. I felt anxious (ANXIOUS)
12. I felt high (HIGH)
13. I felt drowsy (DROWSY)

Responses to items 1, 2, 3, 5, 6, and 7 are summed to produce a "Subjective External Perceptions" composite score. Response to items 4, 8, 9, 10, and 11 are summed to produce a "Subjective Internal Perceptions" composite score. Items 12 and 13 will not be included as they are administered as part of the individual VAS items.

If a response to 1 of the items is missing, the associated composite score will not be calculated.

9.2.3 Drug Similarity VAS

The Drug Similarity unipolar VAS items provide an estimate of how close the drug classes with which drug users have familiarity with are when compared to the test drug. On a scale ranging from "Not at all similar" to "Very similar," subjects are asked to compare a drug they had actually received to a comparison drug they previously declared having familiarity/experience with taking.

A Drug History form is completed during the Screening Phase and used to create a subject-specific Drug Similarity measure for use during the Treatment Phase. Drugs that a subject has not personally experienced often enough to use as a standard of comparison (< 2 lifetime uses of a given drug), will not be included in their questionnaire.

Table 9-6. Description of Drug Similarity Visual Analog Scales

Description	Question Text	Response Anchors
Drug similarity	How similar is the drug you most recently received to ***[drug name]***?	0: Not at all similar 100: Very similar
where the question will be repeated for each ***[drug name]*** *in the following list:*		
▪ Phencyclidine (PCP) ▪ Caffeine ▪ Cocaine (including crack) ▪ Codeine, morphine, oxycodone, hydrocodone, hydromorphone ▪ Ecstasy (MDMA) ▪ Heroin	▪ LSD ▪ Methadone ▪ Nicotine ▪ Placebo ▪ D-amphetamine ("Speed") or methamphetamine	▪ Pseudoephedrine (Sudafed) ▪ Halcion, Xanax, or Valium ▪ Ketamine ("Special K") ▪ THC (marijuana, cannabis, hash)
At the conclusion of the list of specific drugs, a general question will appear:		
Overall Familiarity	How familiar was the effect of the drug you most recently received?	0: Very unfamiliar 100: Very familiar

9.2.4 Addiction Research Center Inventory (ARCI)

The Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Group (MBG), Amphetamine (A), Benzedrine Group (BG), Pentobarbital–Chlorpromazine–Alcohol Group (PCAG), and LSD scales will be administered as scheduled in Table 9-3.

The 49-item ARCI is a shortened version (49 true-false items) compiled by Martin et al. [1] from the 550-item ARCI originally developed by Haertzen. [2, 3] This version contains 5 scales, which measure the following effects: Euphoria - MBG scale; Stimulant effects - Amphetamine (A) scale and Benzedrine Group (BG) scale; Dysphoria - LSD scale; and Sedation - PCAG scale. Subjects indicate their responses by selecting "False" or "True." One point is given for each

response that agrees with the scoring direction on the scale (i.e., True items receive a score of 1 if the answer is "True;" no points are given when the answer is opposite to the scoring direction).

The following scales will be administered:

- *Euphoria:* Morphine-Benzedrine Group (MBG) scale
- *Stimulant effects:* Amphetamine (A) scale, Benzedrine Group (BG) scale
- *Dysphoria:* Lysergic Acid Diethylamide (LSD) scale
- *Sedation:* Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale

The items pertaining to the ARCI scales are presented in Table 9-7.

Table 9-7. ARCI Scales Descriptions

Question	Scale				
	A	PCAG	MBG	BG	LSD
My speech is slurred		T			
I am not as active as usual		T			
I have a feeling of just dragging along rather than coasting		T			
I feel sluggish		T			
My head feels heavy		T			
I feel like avoiding people, although I usually do not feel this way		T			
I feel dizzy		T			
It seems harder than usual to move around		T			
I am moody		T			
People might say that I am a little dull today		T		F	
I feel drowsy		T			F
I am full of energy		F			
Today I say things in the easiest possible way			T		
Things around me seem more pleasing than usual			T		
I have a pleasant feeling in my stomach			T		
I feel I will lose the contentment that I have now			T		
I feel in complete harmony with the world and those about me			T		
I can completely appreciate what others are saying when I am in this mood			T		
I would be happy all the time if I felt as I feel now			T		
I feel so good that I know other people can tell it			T		
I feel as if something pleasant had just happened to me			T		
I would be happy all the time if I felt as I do now			T		F
I feel more clear headed than dreamy		F	T	T	
I feel as if I would be more popular with people today	T		T		

Question	Scale				
	A	PCAG	MBG	BG	LSD
I feel a very pleasant emptiness	T		T		
My thoughts come more easily than usual	T		T	T	
I feel less discouraged than usual	T		T		
I am in the mood to talk about the feelings I have			T	T	
I feel more excited than dreamy	T	F			
Answering these questions is very easy today[a]	T			T	
My memory seems sharper to me than usual	T			T	
I feel as if I could do these tests for hours[a]	T			T	
I feel very patient	T				F
Some parts of my body are tingling	T			T	T
I have a weird feeling	T				T
My movements seem faster than usual				T	
I have better control over myself than usual				T	
My movements seem slower than usual				F	
I find it hard to keep my mind on a task or job				F	
I don't feel like reading anything right now				F	
It seems I'm spending longer than I should on each of these questions					T
My hand feels clumsy					T
I notice my hand shakes when I do these tests[a]					T
I have a disturbance in my stomach					T
I feel an increasing awareness of bodily sensations					T
I feel anxious and upset					T
I have unusual weakness of my muscles					T
A thrill has gone through me one or more times since I started this test		F			T
My movements are free, relaxed, and pleasurable					F

Abbreviations: A = Amphetamine; ARCI = Addiction Research Center Inventory; BG = Benzedrine Group; LSD = Lysergic acid diethylamide; MBG = Morphine-Benzedrine Group; PCAG = Pentobarbital–Chlorpromazine–Alcohol Group.

T = True item

F = False item

a. Question modified slightly for computerized presentation.

Responses to individual items will be included. If one of the individual items is missing, the associated scale(s) score will not be calculated.

9.3 Analysis of Pharmacodynamics Measures

The primary PD endpoint of this study is the maximum (peak) effect (Emax) over 24 hours for Drug Liking ("at this moment"), assessed on a bipolar (0 to 100 points) visual analog scale (VAS). This endpoint will be summarized with descriptive statistics. Placebo will be pooled across all cohorts.

E_{max} as well as T_{max} and TA_AUE of key secondary PD endpoints, Overall Drug Liking, Take Drug Again, and High VAS will be summarized similarly by treatment for the Completer population using descriptive statistics. All PD measures at each time point will be summarized by treatment using descriptive statistics and presented graphically. Derived endpoints will be summarized by treatment and paired difference using descriptive statistics.

A mixed-effects model will be used to compare PD endpoints between Kratom dose levels and placebo for all primary and secondary PD endpoints other than the 12-hour postdose results from Drug Similarity VAS and TE_{max} and TE_{min} endpoints. The model will include dose level as a fixed effect and the baseline score as a covariate [where applicable]. P-values for key components of variance, least-square means (LSmeans), and 95% CI for contrasts will be output for each pairwise comparison for Kratom dose levels versus placebo.

For each PD endpoint, the following comparison will be made:

- Kratom 1 g vs. Placebo
- Kratom 2 g vs. Placebo
- Kratom 4 g vs. Placebo
- Kratom 6 g vs. Placebo
- Kratom 8 g vs. Placebo

The Hodges-Lehmann estimate of the location shift, the asymptotic confidence limits, and the asymptotic standard error estimate will be used to estimate the 95% CIs of TE_{max} and TE_{min} secondary endpoints between the Kratom dose levels and placebo. The asymptotic standard error estimate is based on the length of the CIs. Rank sums and p-values from the Wilcoxon Rank Sum test will also be output.

10 SAFETY ANALYSIS

Safety assessments will include AEs monitoring, laboratory tests, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), ECG assessments, physical examination findings, and C-SSRS.

Unless otherwise specified, all available data will be listed and summary tables for safety assessments will be presented for the safety population.

10.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal clinical laboratory finding, for example), symptom, or disease temporally

associated with the use of an investigational product, whether or not related to the investigational product.

Treatment-emergent AEs (TEAEs) are AEs not present prior to but reported following the exposure to study treatment or AEs already present that worsen in intensity or frequency following exposure to study treatment. All TEAEs will be assigned to the last treatment taken by the subject where the date and time of the last treatment dosing is on or before of the start date and time of the event. Any TEAE started during the follow-up period will be assigned to the last treatment that the subject has taken.

In case that the time of onset or time of resolution is unknown, treatment-emergent or assignment would be determined considering the worst case scenario and/or on case-by-case basis, as deemed appropriate. Treatment-emergent AEs with missing severity or relationship to study treatment will also be classified to the worst case (e.g., severe and/or related, as appropriate) in corresponding summaries.

An overall summary of AEs will be presented by treatment and overall including:

- Number of AEs reported, overall only
- Number of TEAEs reported
- Number (%) of subjects with at least one TEAE
- Number (%) of subjects with at least one study drug-related TEAEs (i.e., those with a relationship classified as ‘Reasonable Possibility’)
- Number (%) of TEAEs by relationship to study treatment (i.e., related or unrelated)
- Number (%) of TEAEs by toxicity grade
- Number of serious AEs (SAEs)
- Number (%) of subjects with at least one treatment-emergent SAE
- Number (%) of subjects with at least one study drug-related treatment-emergent SAE
- Number (%) of subjects with a TEAE leading to discontinuation
- Number (%) of subjects with outcome of death

Frequency tables will be presented by treatment and overall for the following:

- Number (%) of subjects with TEAEs by system organ class (SOC) and preferred term (PT)
- Number (%) of subjects with drug-related TEAEs by SOC and PT

Adverse events that led to discontinuation, SAEs, and adverse events with the outcome of death will be listed.

Severity sssessment for AEs will be graded per the current CTCAE.

10.2 Clinical Laboratory Evaluations

Laboratory data will be presented using units as reported by the clinical laboratory.

The laboratory categories and parameters as defined in the protocol will include the following parameters as shown in Table 10-1:

Table 10-1 Clinical Laboratory Assessments

Clinical Laboratory Test Panel	Description
General biochemistry:	Alanine aminotransferase, albumin, alkaline phosphatase, anion gap, aspartate aminotransferase, bilirubin total, blood urea nitrogen (BUN), BUN/creatinine ratio, calcium, carbon dioxide, chloride, creatinine, (including eGFR calculated using the CKD-EPI equation), glucose, phosphorus, potassium, protein total, sodium, and uric acid
Lipid profile:	Total cholesterol, cholesterol high-density lipoprotein, cholesterol lowdensity lipoprotein and triglycerides
Endocrinology:	FSH[a]
Hematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, and platelet count, red cell distribution width
Serology:	HIV Ag/Ab Combo, Hepatitis B surface antigen and Hepatitis C virus
Urinalysis:	Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
Urine drug screen:	Amphetamines, barbiturates, benzodiazepines, cocaine, fentanyl, MDMA, opiates, oxycodone, phencyclidine and tetrahydrocannabinol
Pregnancy test:	Serum pregnancy test at Screening only and urine pregnancy test at all other scheduled days
Alcohol screen:	Urine alcohol test

Abbreviations: eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus.

a. Performed for females in a postmenopausal state only.

The following listings will be presented:

- All laboratory values by category
- Out-of-range laboratory values
- Clinically significant laboratory values

For protocol-specified laboratory parameters, summary tables on observed and change from baseline values will be presented by treatment and visit for each category, including biochemistry (including lipid profile), hematology, and urinalysis (quantitative data only).

10.3 Vital Signs

Vital signs will include systolic and diastolic blood pressures, pulse rate, respiratory rate, oxygen saturation and body temperature.

The following listings will be presented:

- All vital signs
- Clinically significant vital signs

Summary tables on observed and change from baseline values will be presented by treatment, visit, and/or timepoint.

10.4 Electrocardiograms

The 12-lead ECG data will include ventricular rate, PR, QRS, QT, and QTcF.

The following listings will be presented:

- All ECGs
- Clinically significant ECGs

Summary tables on observed and change from baseline values will be presented by treatment, visit, and/or timepoint.

10.5 Physical Examination Findings

The following listings will be presented:

- All physical examination
- Clinically significant physical examination

10.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire designed for the assessment of suicidal ideation and behavior in adolescents and adults.

To monitor for a history of or for the emergence of suicidal ideation and behavior, subjects will undergo C-SSRS evaluations at Screening, Day -1, Day 3, and at EOS/ET.

The questionnaire must be administered by an Investigator or other individual that is suitably qualified by education or training.

Two versions of the C-SSRS will be used during the study. The “Baseline/Screening” version will be used at Screening, and the “Since Last Visit” version will be used on Day -1, Day 3, and at EOS/ET.

If there is a positive result for suicidality on the C-SSRS (defined by a subject answering “yes’ to questions 4 or 5 on the suicidal ideation portion of the C-SSRS), the subject will be evaluated by an Investigator or medically qualified Sub-Investigator for continuation in the study.

If a subject becomes suicidal during the study, an Investigator or medically qualified Sub-Investigator should provide the appropriate treatment to the subject.

The 5 suicidal ideation scores will be summarized by treatment and visit, e.g., Baseline/Screening (lifetime and last 24 months/2 years), and Since Last Visit (Day -1, Day 3, and EOS/ET). A listing by treatment and subject ID will also be provided.

11 EFFICACY ANALYSIS

There is no efficacy assessment defined in the protocol.

12 INTERIM ANALYSES AND DATA SAFETY MONITORING

No formal interim analyses will be performed; blinded safety and PD data will be reviewed by an Investigator and medical monitor following completion of each kratom dose level.

13 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Not applicable.

14 GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

The formats and layouts of TFLs are provided in a separate document as common displays. Their numbering and general content follow the International Conference on Harmonisation (ICH) E3 guidelines. Actual formats and layouts may be altered slightly from those presented as necessary to accommodate actual data or statistics.

15 REFERENCES

1. Martin WR, Sloan JW, Sapira JD, Jasinski DR. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin Pharmacol Ther 1971;12(2):245–258.
2. Haertzen CA, Hill HE, Belleville RE. Development of the Addiction Research Center Inventory (ARCI): selection of items that are sensitive to the effects of various drugs. Psychopharmacologia 1963;70:155–166.
3. Haertzen CA. An Overview of the Addiction Research Center Inventory (ARCI): An Appendix and Manual of Scales. Rockville, MD: National Institute on Drug Abuse; 1974.

APPENDIX A STUDY SCHEDULE(S)

	Screening	Treatment Period				Follow-Up Visit
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**7 ± 2 (EOS/ET)**
Subject Review						
Informed Consent [1]	X					
Eligibility Criteria Review	X	X	X			
Demographics	X					
Medical History	X	X				
Medication, Recreational Drug, Alcohol, and Nicotine Use History	X	X				
DSM-5 Diagnostic	X					
Safety						
C-SSRS Questionnaire[2]	X	X			X	X
Height, Weight, and BMI[3]	X					X
Blood Pressure, Pulse, Body Temperature, and Respiratory Rate [4]	X	X	X	X	X	X
Continuous SpO_2 Monitoring[5]			X			

[1] The latest version of the consent form must be signed prior to subject's inclusion (prior to study drug administration).

[2] Details presented in Section 6.1.7 of protocol.

[3] At the Follow-Up Visit, only weight and BMI will be measured.

[4] Timepoints of each parameter (blood pressure, pulse, body temperature, and respiratory rate) are detailed in Section 6.1.4.1 of protocol.

[5] Continuous monitoring will be performed up to 1 hour prior to study drug administration and will continue for up to 6 hours following study drug administration, or longer if deemed medically necessary. Additional details are presented in Section 6.1.4.2 of protocol.

	Screening	Treatment Period				Follow-Up Visit
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**7 ± 2 (EOS/ET)**
Spot SpO_2[6]	X		X			
Physical Examination [7]	X	X			X	X
General Biochemistry, Hematology, and Urinalysis [8]	X	X			X	X
Serology[h]	X					
12-lead ECG [9]	X	X	X	X	X	X
Alcohol and Drugs of Abuse Screen[h]	X	X				
Pregnancy Test[h]	X	X			X	X
FSH[h]	X					
AE Monitoring	X	X	X	X	X	X
Concomitant Medication Recording	X	X	X	X	X	X
Pharmacokinetics						
Blood sampling for PK [10]			X	X	X	
Pharmacodynamics						
Training Session[11]		X				

[6] Timepoints are detailed in Section 6.1.4.2 of protocol for spot SpO_2.

[7] A full physical examination will be performed at Screening and at EOS/ET. A symptom-oriented physical examination will be performed as needed at all other timepoints.

[8] Details are provided in Table 9-1.

[9] ECG scheduled timepoints are detailed in Section 6.1.4.5 of protocol.

[10] Blood sampling time points for PK determinations are detailed in Section 6.1.8 of protocol.

[11] Details are presented in Section 6.3 of protocol. Additional training sessions may be conducted as needed.

	Screening	Treatment Period				Follow-Up Visit
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**7 ± 2 (EOS/ET)**
Pupillometry[12]			X	X		
Subjective Measures[13]			X	X		
Confinement and Study Administration						
Admission		X				
Randomization			X			
Study Drug Administration			X[14]			
Discharge [15]					X	

Abbreviations: BMI = body mass index; C-SSRS = Columbia Suicide Severity Rating Scale; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ECG = electrocardiogram; EOS = end of study; ET = early termination; FSH = follicle stimulating hormone; PD = pharmacodynamic; PK = pharmacokinetic; SpO_2 = respiratory rate.

[12] Pupillometry time points for PD evaluations are detailed in Section 6.3.1 of protocol.

[13] Type of subjective measures and timepoints are detailed in Section 6.3.2 of protocol.

[14] Study drug will be administered 30 minutes after the start of a meal as detailed in Section 5.4 of protocol.

[15] Discharge from the clinical site will occur after the 48-hour PK blood sample.