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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Protocol Number:	75F40121C00199
Altasciences Project Number:	FDU-P4-117
Investigational Product:	Kratom 500 mg capsules
Phase of Development:	1
Sponsor:	Food and Drug Administration (FDA), USA 10903 New Hampshire Ave. Silver Spring MD, 20903

COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation and all applicable federal and local regulations.

Protocol Version	Date
1.0 (Original)	**June 05, 2023**

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STUDY SYNOPSIS

Name of Sponsor/Company:	Food and Drug Administration (FDA), USA
Name of Product:	Kratom 500 mg capsules
Title of Study:	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
Study Development Phase:	1
Objectives:	**Primary objective:** 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. **Secondary objectives:** The secondary objectives of the study are: • To evaluate the pharmacokinetics (PK) of mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine following single ascending oral doses of kratom in healthy nondependent recreational polydrug users with opioid experience. • To evaluate the pharmacodynamics (PD) of single ascending oral doses of kratom in healthy nondependent recreational polydrug users with opioid experience.
Endpoints:	**<u>Primary endpoint:</u>** **Safety:** 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). **<u>Secondary Endpoints:</u>** **Pharmacokinetic:** The PK endpoints of this study are the following PK parameters of mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine: maximum observed concentration (C_{max}), time of maximum observed concentration (T_{max}), area under the curve from time 0 to the last measurable observed concentration (AUC_{0-T}), and area under the curve from time 0 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.

	Pharmacodynamic: 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 Addiction Research Center Inventory (ARCI): o Morphine-Benzedrine Group (MBG) Scale (E_{max}, TE_{max}, and TA_AUE) o Amphetamine (A) Scale (E_{max}, TE_{max}, and TA_AUE) o Benzedrine Group (BG) Scale (E_{max}, TE_{max}, and TA_AUE) o Pentobarbital–Chlorpromazine–Alcohol Group (PCAG) Scale (E_{max}, TE_{max}, and TA_AUE) o Lysergic acid diethylamide (LSD) Scale (E_{max}, TE_{max}, and TA_AUE) o Bowdle VAS Internal and External Perceptions composite scores (E_{max}) o Drug Similarity VAS 12-hour postdose scores • Pupillometry o Maximum pupil constriction as assessed by the difference between initial pupil diameter and minimum pupil diameter (MPC)

<table>
<tr><td></td><td>

Time to maximum pupil constriction
Pupillometry area over the curve (time-averaged pupillometry area over the effect curve relative to baseline [TA_PAOC])

</td></tr>
<tr><td>Investigational Product, Dose, and Mode of Administration:</td><td>Kratom 500 mg capsules
Manufacturer: Sun Distribution, Super Organics
Mode of administration: Oral</td></tr>
<tr><td>Placebo and Mode of Administration:</td><td>Placebo-to-match kratom 500 mg capsules
Mode of administration: Oral</td></tr>
<tr><td>Study Population:</td><td>Healthy, male and female nondependent, recreational polydrug users with opioid experience</td></tr>
<tr><td>Planned Number of Subjects:</td><td>A total of 40 subjects (8 subjects in each of the 5 cohorts) will be included.</td></tr>
<tr><td>Study Design:</td><td>This single center, single-dose, randomized, adaptive, double-blind, placebo-controlled study will consist of 5 single ascending dose (SAD) cohorts. The sample dose levels by cohort are as follows:
<table>
<tr><th>Cohort</th><th>Number of Subjects (active:placebo)</th><th>Dose[a]</th><th>Regimen</th></tr>
<tr><td>1</td><td>8
(6:2)</td><td>1 g (2 capsules)</td><td rowspan="5">Single oral administration of kratom or placebo on Day 1</td></tr>
<tr><td>2</td><td>8
(6:2)</td><td>E.g., 2 g (4 capsules)</td></tr>
<tr><td>3</td><td>8
(6:2)</td><td>E.g., 4 g (8 capsules)</td></tr>
<tr><td>4</td><td>8
(6:2)</td><td>E.g., 6 g (12 capsules)</td></tr>
<tr><td>5</td><td>8
(6:2)</td><td>E.g., 8 g (16 capsules)</td></tr>
</table>
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 in the table above, 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.

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.

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.</td></tr>
<tr><td>Duration of Treatment and Subject Confinement:</td><td>Duration of clinical trial (per subject):
Screening: Day -28 to Day -1 (up to 28 days)</td></tr>
</table>

	Treatment period: 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. Total study duration: up to 37 days (including screening)
Safety Meetings for Dose Escalation and Adjustments:	Following completion of each cohort, a Safety Review Committee will review all safety and PD data to evaluate progression to the next dose cohort. The Safety Review Committee 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. Dose levels presented are approximations and may be increased or decreased based on interim safety reviews. The upper dose may exceed 8 g if deemed appropriate and safe by interim data reviews.
Bioanalysis:	Mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine plasma concentrations will be measured by validated bioanalytical methods.
Safety Analysis:	Clinical laboratory tests, AEs, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), ECG findings, physical examination findings, and C-SSRS will be used to perform safety analyses. Safety analyses will be fully detailed in the statistical analysis plan (SAP).
Pharmacokinetic Analysis:	The PK parameters C_{max}, C_{max}/D, T_{max}, AUC_{0-T}, AUC_{0-T}/D, $AUC_{0-\infty}$, $AUC_{0-\infty}/D$, $AUC_{T/\infty}$, λ_Z, and T_{half} will be estimated for mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine. Additional parameters may be calculated. The PK analyses will be performed by non-compartmental analysis. The PK analysis will be detailed in the SAP.
Pharmacodynamic Analysis:	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. 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. 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. 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}/TE_{min} 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. The PD analysis will be fully detailed in a SAP.
Statistical Analysis:	The statistical analysis will be fully detailed in a SAP.

STUDY ADMINISTRATIVE STRUCTURE

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PHARMACOKINETIC AND STATISTICAL FACILITY:	Altasciences 575 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4B3
DATA MANAGEMENT FACILITY:	Altasciences 575 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4B3
PROJECT MANAGEMENT:	Altasciences 575 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4B3
COGNITIVE TESTS:	Cambridge Cognition 2750 Rasmussen Road Park City Utah 84098, USA

1. INTRODUCTION

1.1. Study Rationale

The Food and Drug Administration (FDA) has previously warned consumers about the use of kratom (*Mitragyna speciosa*). Kratom has both affinity and activity at mu opioid receptors, receptor sites known to be associated with abuse. Although kratom use is prevalent, to date, clinical evaluations of abuse potential have not been performed. The Controlled Substance Staff (CSS) at FDA is proposing to initiate a pilot, single ascending dose (SAD) study of botanical kratom. Currently there are limited safety data and chemical, manufacturing, and control data to support clinical research with botanical kratom and isolated kratom alkaloids. The present study will provide data in these areas that will inform future clinical research with kratom.

The dose escalation will include 5 cohorts (8 subjects per cohort) of subjects randomized to receive either active drug (kratom) or placebo (6:2 active:placebo). Following each dosing, safety and pharmacodynamic (PD) data will be reviewed by a safety review board to determine if further dose escalation can safely commence.

A placebo control is used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment as well as to minimize subject and investigator bias. Blinded treatment, including the use of double-blind procedures, will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The FDA guidance "Bioavailability Studies Submitted in NDAs or INDs — General Considerations" recommends conducting studies under fed conditions if tolerability issues or serious adverse events (SAEs) are anticipated under fasted conditions. The current study will therefore administer the study drug following intake of a high-fat breakfast to avoid potential tolerability issues (i.e., vomiting).

Subjects will be healthy individuals, with previous non-therapeutic (recreational) polydrug use and opioid experience. Furthermore, subjects will be required to have experience with drugs that have psychoactive properties, particularly since supratherapeutic (high) doses of kratom will be evaluated in this study.

In addition to the requirement that subjects be "history qualified" (i.e., have a history of recreational opioid use), medical history and clinical assessments will also be used to confirm that subjects meet the required study eligibility criteria and to confirm that they are not dependent on drugs or alcohol. Urine drug screens and alcohol checks, as well as other assessments (e.g., pregnancy tests) will be used to confirm compliance and eligibility.

1.2. Background

Kratom is a botanical product that contains a mixture of indole-based alkaloid compounds. Though at least 25 alkaloid compounds have been isolated from kratom, most represent only a small portion of the total alkaloid content (≤1%) and thus, depending on their potency, may not significantly contribute to the overall effects of kratom individually.[2] Mitragynine represents 66% of the total extractable alkaloid content of kratom, with paynantheine (9%), speciogynine (7%), and 7-hydroxymitragynine (2%) being the next most abundant. Of note, 7-hydroxymitragynine is thought to be the most potent of these compounds with regard to psychoactive effects.[2] Paynantheine and speciogynine have been reported to exhibit high affinity

for the 5-HT_{1A} and 5-HT_{2B} serotonin receptors and produce antinociception in rats, via an opioid-receptor independent mechanism that was blocked by a 5-HT_{1A} receptor antagonist.[3] Thus, while mitragynine and 7-hydroxymitragynine are thought to mediate most of kratom's pharmacologic effects, the presence of other minor alkaloid compounds may contribute to the overall effect of kratom use and may do so through multiple pharmacologic pathways.[1]

The kratom plant, *M. speciosa*, is a member of the coffee family and is native to many countries in Southeast Asia, including but not limited to Thailand, Malaysia, New Guinea, and the Philippines. For many centuries, the leaves of this plant have been used in Southeast Asia for cultural, recreational, health, and medicinal purposes. The leaves are most often chewed or dried and made into tea. Kratom uses vary widely; users seek desired benefits that range from calming effects to stimulative effects.[1,4,5]

While there are extensive reports in the literature regarding the use of kratom in the US, Malaysia, and Thailand, overall, the available clinical literature is not strong. Most of the published studies on kratom use are not controlled or prospective. There are very few studies directly correlating specific doses of kratom with adverse effects. Rather, there are a large number of case reports available. However, many of the patients described in these cases had a history of chronic kratom use, consumed large amounts of kratom, and/or used multiple substances simultaneously. The case reports cover the years 2010 to 2021. There are a fair number of studies reported in the literature, but they are mostly retrospective analyses of poison center databases, case study series, autopsies, and social media posts, as well as survey (self-reported information) and interview (conducted by trained professional) studies. There are a few small prospective pharmacokinetics studies and in vitro pharmacokinetics studies. The reported studies cover the years 1998-2021.[1]

The available literature describing human PK and metabolism studies with kratom are summarized in the Investigator's Brochure of kratom.[1]

1.3. Rationale for Dose Selection

Human abuse potential studies investigate a range of doses from the highest proposed therapeutic dose to supratherapeutic doses (2-3× highest therapeutic dose, if it can be done safely). In order to determine an appropriate kratom dose range for a future human abuse potential study, kratom will first be evaluated in this dose escalation study to examine the safety, tolerability, PK, and PD effects in the intended study population (healthy nondependent recreational polydrug users with opioid experience). Based on published epidemiological papers, doses of kratom used for medical or non-medical purposes range widely from 1 to 12 g. Doses below 6 g are typically considered low doses, whereas doses over 6 g are considered high doses. Doses in excess of 7 to 8 g are considered to produce strong sedation and analgesia effects, whereas lower doses < 5 g are reported as producing stimulant-like effects .[6] To evaluate the full range of PD effects, up to 5 dose levels will be evaluated starting with a low dose (1 g) and escalating to approximately 8 g to evaluate the pharmacological properties of kratom. Doses may exceed 8 g if it is deemed safe based on interim safety reviews. Doses will be adjusted as needed between cohorts based on review of safety and PD data.

1.4. Risk/Benefit Assessment

1.4.1. Known Potential Risks

The true incidence of adverse reactions associated with the use of kratom is difficult to determine, due to the lack of randomized, controlled clinical studies. However, the adverse events (AEs) most commonly reported related to kratom use, in 10% or more of populations identified in published, peer-reviewed articles, are as follows: acute kidney injury, agitation, altered consciousness, anxiety, apathy, appetite loss, blood pressure increase (delayed onset), confusion, constipation, diaphoresis/feeling hot, depression, dizziness, drowsiness/lethargy/fatigue, dyspnea, hallucinations, headaches, heart rate increase (delayed onset), hypotension, hypertension, insomnia, feeling intoxicated, irritability, elevated low-density lipoprotein and high-density lipoprotein, libido/sexual performance decrease, miosis, decreased motivation, mydriasis, nausea, palpitation, physical pain, respiratory failure, stomach ache/abdominal pain, tachycardia, tongue numbness, tremor, weight loss, and vomiting.[1]

The doses of kratom administered in this study are not anticipated to induce unmanageable risks to the subjects. The safety monitoring practices employed in this protocol (i.e., AE questioning, clinical laboratory assessments, 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]) are appropriate to protect the subjects' safety and should detect treatment--emergent AEs (TEAEs).

1.4.2. Known Potential Benefits

As the study treatments are not being given to subjects to treat a medical disorder, there will be no direct medical benefit from participation in this trial.

2. STUDY OBJECTIVES AND ENDPOINTS

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

Table 2-1. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
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 AEs, laboratory tests, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), ECGs, physical examination findings, and C-SSRS.
Secondary	
To evaluate the PK of mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine 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-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine: C_{max}, T_{max}, AUC_{0-T}, and $AUC_{0-\infty}$. Additionally, dose-normalized PK parameters C_{max}/D, AUC_{0-T}/D, and $AUC_{0-\infty}/D$ will be estimated.

To evaluate the 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) 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
	  ○ 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
	  ○ Good Effects VAS (E_{max}, TE_{max}, and TA_AUE)
	  ○ High VAS (E_{max}, TE_{max}, and TA_AUE)
	• Negative Effects
	  ○ Bad Effects VAS (E_{max}, TE_{max}, and TA_AUE)
	• Other Subjective Effects

OBJECTIVES	ENDPOINTS
	○ Any Effects VAS (E_{max}, TE_{max}, and TA_AUE) ○ Feeling Drunk VAS (E_{max}, TE_{max}, and TA_AUE) ○ Drowsiness/Alertness VAS (E_{max}, TE_{max}, E_{min}, TE_{min}, and area over and under the effect-time curve [TA_AOE, TA_AUE]) ○ Relaxation/Agitation (E_{max}, TE_{max}, E_{min}, TE_{min}, TA_AOE, and TA_AUE) ○ ARCI MBG Scale (E_{max}, TE_{max}, and TA_AUE) ○ ARCI A Scale (E_{max}, TE_{max}, and TA_AUE) ○ ARCI BG Scale (E_{max}, TE_{max}, and TA_AUE) ○ 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])

Abbreviations: AE = adverse event; ARCI = Addiction Research Center Inventory; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; LSD = Lysergic acid diethylamide; MBG = Morphine-Benzedrine Group; MPC = minimum pupil diameter; PCAG = Pentobarbital–Chlorpromazine–Alcohol Group; PD = pharmacodynamic; PK = pharmacokinetic; VAS = visual analog scale.

3. STUDY DESIGN

3.1. Overall Study Design

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.

The schedule of activities of the study is described in Table 6-1.

3.2. Adaptive Features and Risk Management of Study Design

The rational of having the following adaptive features is based on the hypothesis-forming approach of this clinical trial. The features from Table 3-2 may be adapted during the study.

Table 3-2. Adaptive Features and Boundaries

Adaptive study design category	Adaptive Features	Boundaries
Dose level for cohorts	Dose levels may be adjusted	Doses are intended to escalate, however, they may be adjusted to higher or lower doses on the basis of safety, tolerability, and PD data reported in the previous cohort(s).

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic.

Decision-making process for the above adaptive study categories will be as follows:

- Interim review of safety and tolerability of kratom and emerging data (PD) from completed or ongoing cohorts in a blinded fashion by the SRC.
- Outcome on the adaptive study category will be documented by the SRC.

Based on the above, implementation can be performed without delay and Research Ethic Committee approval. If any adaptive features are outside the above pre-specified boundaries, Research Ethic Committee approval is mandatory before implementation.

3.3. Maximum Tolerated Dose

The Maximum Tolerated Dose (MTD) definition: Transient, mild or moderate AEs occurring at a given dose level will be evaluated by the SRC prior to dose escalation. If such AEs occurred in ≥ 3 subjects at a given dose level, dose escalation may be ceased and this dose level or the next lower one will be considered the MTD, or an intermediate dose level can be investigated. If such AEs occurred in ≤ 2 subjects depending on the particular adverse effects observed, the current dose level may be considered the MTD, or dose escalation may proceed.

4. SUBJECT POPULATION

Subjects meeting all the inclusion criteria and none of the exclusion criteria at Screening may be eligible for participation in this study. Continued eligibility will be assessed upon admission to the clinical site, prior to study drug administration.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study.

4.1. Inclusion Criteria

1. Provision of signed and dated informed consent form (ICF)

2. Stated willingness to comply with all study procedures and availability for the duration of the study

3. Healthy adult male or female

4. Current nondependent, polydrug recreational user who has used opioid drugs for recreational (nontherapeutic) purposes (i.e., for psychoactive effects) at least 10 times in the subject's lifetime and at least once in the last 12 weeks from Screening; and has a history of recreational use of at least 2 or more of any of the perception-altering (e.g., lysergic acid diethylamide [LSD], kratom, cannabis, dronabinol, ketamine, phencyclidine [PCP], dextromethorphan, 3,4 methylenedioxymethamphetamine [MDMA], mescaline, psilocybin, tryptamine derivatives or ring-substituted amphetamines with perception altering effects) or stimulant (e.g., cocaine, amphetamine, methamphetamine, methylphenidate, methcathinone, and other synthetic cathinones) drugs on at least 5 occasions in the subject's lifetime

5. If male, meets one of the following criteria:

   a) Is able to procreate and agrees to use one of the accepted contraceptive regimens and not to donate sperm from study drug administration to at least 90 days after study drug administration. An acceptable method of contraception includes one of the following:

      - Abstinence from heterosexual intercourse
      - Double-barrier method (e.g., male condom with spermicide or male condom with a vaginal spermicide [gel, foam, or suppository])

   Or

   b) Is unable to procreate; defined as surgically sterile (i.e., has undergone a vasectomy at least 180 days prior to study drug administration)

6. If female, meets one of the following criteria:

   a) Is of childbearing potential and agrees to use an acceptable contraceptive method. Acceptable contraceptive methods include:

      - Abstinence from heterosexual intercourse from the Screening visit through to at least 30 days after study drug administration

      or

      - One of the following contraceptive methods, used from at least 28 days prior to the Screening visit through to at least 30 days after study drug administration:
        - Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, or transdermal patch)
        - Intrauterine device (with or without hormones)
        - Male partner vasectomized at least 6 months prior to the Screening visit

      or

      - One of the following double-barrier contraceptive methods, used from the Screening visit through to at least 30 days study drug administration:

- Male condom plus spermicide
- Diaphragm plus spermicide
- Cervical cap plus spermicide

Or

b) Is of non-childbearing potential, defined as surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation), or is in a postmenopausal state (i.e., at least 1 year without menses without an alternative medical condition prior to the Screening visit and follicle stimulating hormone levels ≥ 40 mIU/mL at Screening)

7. Aged at least 18 years but not older than 59 years (inclusive) at Screening

8. Body mass index (BMI) within 18.0 kg/m^2 to 34.0 kg/m^2, inclusively at Screening

9. Minimum weight of 50.0 kg at Screening

10. Have no clinically significant diseases captured in the medical history or evidence of clinically significant findings on the physical examination (including vital signs, oxygen saturation [SpO_2], and respiratory rate) and/or ECG, as determined by an Investigator

4.2. Exclusion Criteria

1. Difficulty swallowing capsules

2. Female who is lactating

3. Female who is pregnant according to the pregnancy test at Screening or prior to study drug administration

4. Male with female partner who is pregnant, lactating, or planning to become pregnant during this study or within 90 days after study drug administration

5. History of significant hypersensitivity to kratom or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs

6. Presence or history of significant gastrointestinal, liver or kidney disease, or surgery that may affect drug bioavailability with the exception of cholecystectomy that is permitted at the discretion of an Investigator

7. History of significant hepatic, renal, cardiovascular, pulmonary, hematologic, neurological, psychiatric, gastrointestinal, endocrine, immunologic, ophthalmologic, or dermatologic disease

8. Presence of any significant respiratory illness or presence or history of chronic respiratory disease (e.g., upper respiratory illness, sleep apnea, emphysema, asthma) at Screening (subjects with acute respiratory illness may be rescheduled upon resolution at the discretion of an Investigator)

9. History of substance or alcohol moderate to severe use disorder (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)

10. Is a heavy smoker (> 20 cigarettes per day) and/or is unable to abstain from smoking or unable to abstain from the use of prohibited nicotine-containing products for at least 1 hour before and 8 hours after study drug administration (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges)

11. Regularly consumes excessive amounts of caffeine or xanthines, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, or other caffeinated beverages per day

12. History of suicidal behavior within 2 years of Screening, showing suicidal tendency as per the C-SSRS administered at Screening (APPENDIX 7), or is currently at risk of suicide in the opinion of an Investigator

13. Presence of clinically significant ECG abnormalities at the Screening visit, as defined by medical judgment. Note: QT corrected according to Fridericia's formula (QTcF) interval of > 450 msec in male subjects or > 470 msec in female subjects will be exclusionary. The ECG may be repeated once for confirmatory purposes if the initial value obtained exceeds the limits specified.

14. Estimated glomerular filtration rate (eGFR) ≤ 60 mL/min as calculated by the CKD-EPI equation

15. Any clinically significant illness in the 28 days prior to study drug administration

16. Use of any prescription drugs (with the exception of hormonal contraceptives or hormone replacement therapy) in the 28 days prior to study drug administration, that in the opinion of an Investigator would put into question the status of the participant as healthy

17. Use of St. John's wort in the 28 days prior to study drug administration

18. Positive test result for alcohol and/or drugs of abuse at admission (prior to study drug administration). Subjects with positive results at admission may be rescheduled at the discretion of an Investigator. If tetrahydrocannabinol (THC) is positive at admission a cannabis intoxication evaluation will be done by an Investigator and subjects may be permitted to continue in the study at the discretion of an Investigator. Other positive test

results should be reviewed to determine if the subject may be rescheduled, in the opinion of the investigator.

19. Positive screening results to HIV Ag/Ab combo, hepatitis B surface antigen or hepatitis C virus tests

20. Any other clinically significant abnormalities in laboratory test results at Screening that would, in the opinion of an Investigator, increase the subject's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data

21. Inclusion in a previous group for this clinical study

22. Intake of kratom in the 14 days prior to study drug administration

23. Intake of an Investigational Product (IP) in the 28 days prior to study drug administration

24. Donation of plasma in the 7 days prior to study drug administration

25. Donation of 1 unit of blood to American Red Cross or equivalent organization or donation of over 500 mL of blood in the 56 days prior to study drug administration

26. Subject cannot eat dairy and/or is lactose intolerant

27. Is, in the opinion of an Investigator or designee, considered unsuitable or unlikely to comply with the study protocol for any reason

4.3. Withdrawal Criteria

4.3.1. Before First Treatment Administration

Before the first treatment administration, inclusion/exclusion criteria will govern the subjects to be dosed. Subjects withdrawn before first treatment administration will not be followed up and will not undergo End-of-Study/Early Termination assessments. Other safety assessments may be performed if required.

Subjects are free to withdraw their consent to participate in the study at any time, without prejudice. The reason for their withdrawal or for deciding to end their participation will be documented.

4.3.2. After First Treatment Administration

Subjects may, at any time, voluntarily withdraw from the study or be removed from the study at the discretion of an Investigator or Sponsor. An Investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject or if their behavior is deleterious to the study environment. If such withdrawal occurs, or if the subject fails to return for visits, an Investigator should determine the primary reason for a

subject's premature withdrawal from the study and record the reason in the subject's study documents.

An Investigator may remove a subject from the study on the recommendation of the PK facility and/or Sponsor due to an unanticipated event that could result in an inadequately characterized PK profile (e.g., a missed blood draw, an AE, meal deviation, concomitant medication intake, etc).

In the case of a clinically significant illness detected during the trial (including Coronavirus Disease 2019 [COVID-19] diagnosis), the Principal Investigator (or delegate) will, in concert with the Sponsor, determine the most appropriate course of action on an individual basis. Evaluations will include but are not limited to:

- The safety of the subject and other study participants
- The possible effect the illness would have on the results gathered during the trial, and their ability to be appropriately analyzed or interpreted
- The possibility of suspending participation then re-initiating it after recovery
- The implication of any inclusion or exclusion criteria that would contradict possible actions
- The implication of any adherence to regulatory guidelines that may be affected by actions decided; for example group effect analysis
- The sample size calculation, current number of subjects, and possibility of replacement subjects

Evaluations and decision-making for subject removal will be documented in the study file, reported to the Sponsor, and discussed where appropriate in the Clinical Study Report.

Attempts should be made to have such subjects complete the End-of-Study/Early Termination assessments. End-of-Study/Early Termination assessments should be performed as soon as possible after the last study treatment administration.

For subjects lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), an Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

4.3.2.1. Stopping Rules

4.3.2.1.1. Individual Subject Stopping Rules

Participation in the clinical study may be discontinued by an Investigator (or delegate) in charge of the study or by the Sponsor for any of the following reasons, but not limited to:

- AEs (including if a subject develops any significant illness or needs to undergo any major surgery during course of the study) or laboratory abnormalities that would put the subject at risk to continue in the opinion of the Investigator and/or the Sponsor

- Subject non-compliance (including any violation of protocol requirements which may affect the study outcome)

4.3.2.1.2. Cohort Stopping Rules

If any of the following safety concerns are observed, dosing of all subjects at the given dose level or higher will be suspended/halted and all available data will be evaluated by the SRC. Dose continuation (remaining subjects within a cohort or remaining dosing for a subject) or escalation should not proceed for any of, but not limited to, the following reasons:

- If 1 kratom-related SAE occurs in a cohort
- Moderate or severe AEs in 50% of the subjects in the cohort or more

Dose escalation will be discussed during the SRC meeting and may be stopped depending on Principal Investigator's or Sponsor's decision.

4.3.2.1.3. Trial Stopping Rules

Clinical trial stopping rules:

- If 2 kratom-related SAEs occur in a cohort
- Occurrence of 1 death attributable to kratom

4.4. Lifestyle and/or Dietary Requirements

- Subjects will be prohibited from consuming food or beverages containing grapefruit and/or pomelo for 7 days prior to dosing and during the study.
- Subjects will be prohibited from consuming alcohol for 48 hours prior to dosing and during the study. Throughout the study (including the Follow-Up Visit), in case of any doubt about alcohol consumption, a test for alcohol may be performed if requested by an Investigator.
- Subjects will be prohibited from consuming food or beverages containing xanthines (i.e., tea, coffee, cola drinks, energy drinks or chocolate) for 48 hours prior to dosing and during the study.
- Subjects will be prohibited from consuming all recreational drugs (including cannabis) from the time of screening and for the duration of the study.
- Subjects will eat only the food provided by the study site during confinement at the clinical site.
- During the study, subjects who are smokers should not smoke more than the equivalent of 20 cigarettes per day. Subjects will abstain from smoking for 1 hour prior to and until 8 hours after study drug administration.
- Subjects will be asked to refrain from driving, operating machinery, or engaging in hazardous activities until they and an Investigator are convinced the study drug is not impairing their judgment and/or ability to perform skilled tasks.

- Female subjects of childbearing potential will have to take appropriate measures to prevent pregnancy as described in Section 4.1. It is the participant's responsibility to notify the clinical site if a pregnancy occurs from the end of their study participation until 30 days after study drug administration.
- Male subjects will be expected to use an acceptable contraceptive regimen and not to donate sperm as described in Section 4.1.

4.5. Concomitant Treatment

In addition to the drugs prohibited as per the exclusion criteria (Section 4.2), subjects will also be prohibited from taking any over-the-counter products for 7 days prior to dosing and during the study, unless deemed acceptable by an Investigator.

Except for medication which may be required to treat AEs, no other treatment or medication other than the study drugs will be allowed from the first dosing until all study activities and evaluations have been completed.

Systemic contraceptives and hormone replacement therapy are permitted for female subjects.

Subjects will be instructed to notify the study site about any new medications taken after the start of the study treatment. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has received the study treatment must be listed in the subject case report form (CRF). The drug name and dose taken will be noted. An Investigator or delegate and/or the Sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc.

5. STUDY TREATMENTS

5.1. Investigational Products

All IPs will be provided by the Sponsor.

5.1.1. 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.

5.1.2. 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.

5.2. Investigational Product Management

5.2.1. Packaging, Labeling and Dispensing

The Sponsor will be responsible for ensuring that the IPs are manufactured in accordance with applicable current Good Manufacturing Practice regulations and requirements.

The IPs will be labeled according to the requirements of local law and legislation. The IPs will be dispensed by the clinical site's pharmacy, unless the Sponsor supplies the pharmacy with prelabeled individual dosing samples.

5.2.2. Storage and Handling

All study drugs will be shipped from the client or client resources to the clinical site's pharmacy. Storage and handling conditions are described in the Investigator's Brochure of kratom.[1]

The clinical site's pharmacy will maintain an inventory record of the IPs received, stored (in a secure restricted area), and dispensed. IPs will be provided to study subjects only.

5.2.3. Method of Assigning Subjects to Treatment Groups

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.

5.2.4. Blinding

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.

5.2.5. Study Drug Accountability

Complete and accurate inventory records of all study drugs will be maintained. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product.

At the conclusion of the study, all unused IPs and all medication containers will be returned to the Sponsor unless the Sponsor has approved other arrangements. Drug accountability will be performed at the completion of the trial.

5.3. Administration of Study Drug

Study drug will be administered in the morning. The date and time of each dose will be recorded. For each subject, all scheduled postdose activities and assessments will be performed relative to the time of study drug administration.

Thirty (30) minutes after the start of a high-fat breakfast (refer to Section 5.4 for details), an oral dose of the assigned formulation will be administered to subjects with approximately 240 mL of water at ambient temperature. Considering the high number of capsules to be taken for certain cohorts, an additional 240 mL of water will be allowed if required. Time of dosing will be set equal to the time when the first capsule is administered to the subject. The complete dosing procedure must be completed within 5 minutes. Dosing procedures done up to 2 minutes outside the allowed time window will not be considered as protocol deviations but will be documented. The start and end times, as well as the volume of water ingested during drug administration will be recorded. The capsules must be swallowed whole and must not be chewed or broken.

5.3.1. Treatment Compliance

The study drugs will be dispensed only to eligible subjects and administered under the supervision of study personnel. Treatment compliance will be verified according to the site's standard operating procedures (SOPs).

5.4. Meals

Food intake will be controlled during the confinement period and for all subjects.

Following an overnight fast of at least 10 hours, subjects will receive a standardized high-fat meal 30 minutes before drug administration. The meal will consist of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. Substitutions in this test meal may be made provided that the meal delivers a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and texture. Subjects must eat the total content of this meal in 30 minutes or less. A subject who eats less than 75% of the high-fat meal will be removed from the study. A standardized lunch will be served at least 4 hours after dosing.

5.5. Fluids

Fluid intake other than water will be controlled during the confinement period and for all subjects.

Water will be permitted as needed except from 1 hour predose until 1 hour after dosing.

5.6. Other Protocol Restrictions

Subjects will not engage in strenuous activity at any time during the confinement periods.

6. STUDY PROCEDURES

An overview of the study activities for each participant is detailed in Table 6-1.

Subjects may leave the clinical site 48 hours following drug administration. However, they may be advised to stay at the clinical site for safety reasons, if judged necessary by an Investigator or delegate in charge. Subjects will return to the clinical site for a Follow-Up Visit on Day 7 ± 2.

Unless otherwise stated in the protocol, the SOPs of the study facilities, which are available for all activities relevant to the quality of the study, will be followed during this study. When the nominal time for multiple events occurs simultaneously, the events will be staggered using their acceptable windows (acceptable windows for each assessment are specified in the following sections of this protocol). When timepoints coincide, procedures should be carried out in the following order:

1. Vital signs (prior to nominal time)
2. ECG (prior to nominal time)
3. PK blood sampling (at nominal time)
4. Pupillometry (following nominal time, immediately following PK blood sampling and prior to other PD assessments)
5. Subjective measures (following nominal time, immediately following pupillometry)

Any deviation from protocol procedures should be noted in the source documentation and compiled for reporting in the Clinical Study Report.

Table 6-1. Schedule of Activities

	Screening	Treatment Period				Follow-Up Visit
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**7 ± 2 (EOS/ET)**
Subject Review						
Informed Consent [a]	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[b]	X	X			X	X
Height, Weight, and BMI[c]	X					X
Blood Pressure, Pulse, Body Temperature, and Respiratory Rate [d]	X	X	X	X	X	X
Continuous SpO_2 Monitoring[e]			X			
Spot SpO_2[f]	X		X			
Physical Examination [g]	X	X			X	X

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

[b] Details presented in Section 6.1.7.

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

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

[e] 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.

[f] Timepoints are detailed in Section 6.1.4.2 for spot SpO_2.

[g] 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.

	Screening	Treatment Period				Follow-Up Visit
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**7 ± 2 (EOS/ET)**
General Biochemistry, Hematology, and Urinalysis [h]	X	X			X	X
Lipid Profile[h]	X					X
Serology[h]	X					
12-lead ECG [i]	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 [j]			X	X	X	
Pharmacodynamics						
Training Session[k]		X				
Pupillometry[l]			X	X		
Subjective Measures[m]			X	X		
Confinement and Study Administration						
Admission		X				
Randomization			X			

[h] Details are provided in APPENDIX 6.
[i] ECG scheduled timepoints are detailed in Section 6.1.5.
[j] Blood sampling time points for PK determinations are detailed in Section 6.2.
[k] Details are presented in Section 6.3. Additional training sessions may be conducted as needed.
[l] Pupillometry time points for PD evaluations are detailed in Section 6.3.1.
[m] Type of subjective measures and timepoints are detailed in Section 6.3.2.

	Screening	Treatment Period				Follow-Up Visit
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**7 ± 2 (EOS/ET)**
Study Drug Administration			X[n]			
Discharge [o]					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.

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

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

6.1. Safety Assessments

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. At the discretion of an Investigator, additional safety assessments may be performed as needed to ensure subject safety.

An Investigator or delegate in charge will be present at the clinical site for at least the first 4 hours following drug administration and will remain available at all times throughout the study.

6.1.1. Medical History

The medical history at Screening will include all queries by the medical and clinical staff related to the subject's well-being and history of relevant past medical events/experiences. Medical history will include all demographic data (age, sex, race, body weight, height, and BMI) and baseline characteristics. Alcohol and smoking habits will also be recorded.

6.1.2. Medication, Recreational Drug, Alcohol, and Nicotine Use History

6.1.2.1. Medication Use

Medication history will be collected as scheduled in Table 6-1.

6.1.2.2. Recreational Drug Use

A lifetime history of all recreational drug use will be collected as scheduled in Table 6-1. History, including drug preference (i.e., drug of choice), frequency of use, and date of last use will be collected using reported drug names and drug class (e.g., cannabinoids, depressants, dissociative anesthetics, hallucinogens, opioids, and morphine derivatives, and stimulants).

The DSM-5 modules will be included as a part of the recreational drug use history and used to screen for substance disorder.

6.1.2.3. Alcohol and Nicotine Use

A lifetime history of alcohol and nicotine use will be collected as scheduled in Table 6-1. History, amount, and frequency of use will be collected.

DSM-5 modules will be included as a part of the alcohol use history and used to screen for alcohol disorder.

6.1.3. Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as outlined in Table 6-1.

The full physical examination will include a general review of the following body systems (at minimum): head and neck, cardiovascular, respiratory, gastrointestinal, brief neurological and general appearance, unless a symptom-oriented physical exam is indicated.

6.1.4. Vital Signs

Windows for blood pressure, pulse, body temperature, spot SpO_2, and respiratory rate assessments are presented in Table 6-2. Vital signs will be performed after the subject is in supine position for at least 3 minutes.

Table 6-2. Acceptable Windows for Vital Sign (Blood Pressure, Pulse, Body Temperature, Spot Oxygen Saturation, and Respiratory Rate) Assessments

Elapsed Time	Acceptable Window
Predose	Within 60 minutes prior to study drug administration
> 0 hour and ≤ 24 hours	± 30 minutes
> 24 hours and ≤ 48 hours	± 1 hour

6.1.4.1. Blood Pressure, Pulse, Body Temperature, Respiratory Rate

Blood pressure, pulse, body temperature, and respiratory rate measurements will be measured as outlined in Table 6-1 and are further detailed in Table 6-3.

Table 6-3. Vital Sign (Blood Pressure, Pulse, Body Temperature, and Respiratory Rate) Recording Schedule

Vital Sign Recording - Scheduled Time Points	Detail of Measures
Screening	Blood pressure, pulse rate, body temperature, and respiratory rate
Day -1	Blood pressure, pulse rate, and body temperature
Day 1: predose	Blood pressure, pulse rate, body temperature, respiratory rate
Day 1: 1, 2, 4, and 6 hours postdose	Blood pressure, pulse rate, and respiratory rate
Day 2: 24 hours postdose	Blood pressure and pulse rate
Day 3: 48 hours postdose	Blood pressure and pulse rate
Follow-up visit/End of Study	Blood pressure and pulse rate

6.1.4.2. Continuous and Spot Oxygen Saturation

Continuous and spot SpO_2 monitoring will be performed as outlined in Table 6-1. Spot SpO_2 will be measured using a portable pulse oximeter placed on the subject's fingertip.

SpO_2 will be monitored for alarms set at <90% continuously 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. In addition, SpO_2 will be recorded at the timepoints scheduled in Table 6-4.

Table 6-4. Spot Oxygen Saturation Schedule

Spot Oxygen Saturation - Scheduled Time Points
Screening
Day 1: predose and approximately 1, 2, 3, 4, 6, 7, 8, 10, and 12 hours postdose

6.1.5. 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed as outlined in Table 6-1. Electrocardiogram measurements are further detailed in Table 6-5. Subjects will be in supine position for at least 3 minutes prior to ECG measurements.

Table 6-5. Electrocardiogram Recording Schedule

Electrocardiogram Recording - Scheduled Time Points
Screening
Day -1
Day 1: 1 and 4 hours postdose
Day 2: 24 hours postdose
Day 3: 48 hours postdose
Follow-up visit/End of Study

Windows for ECG assessments are presented in Table 6-6.

Table 6-6. Acceptable Windows for Electrocardiogram Assessments

Elapsed Time	Acceptable Window
> 0 hour and ≤ 24 hours	± 30 minutes
> 24 hours and ≤ 48 hours	± 1 hour

6.1.6. Laboratory Evaluations

Laboratory evaluations will be performed as outlined in Table 6-1.

The laboratory evaluations to be conducted for this study are presented in APPENDIX 6. Additional clinical laboratory tests may be performed by the medical laboratory as part of larger standard test panels (not required for subject safety).

The Investigator or delegate in charge will assess each abnormal value to determine if it is clinically significant. Postdose clinically significant laboratory values will be reported as AEs, if applicable, as judged by the Investigator or delegate in charge.

Only test results required by the protocol and/or abnormal results will be entered in the clinical database and reported in the Clinical Study Report, based on report requirement.

6.1.7. 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 the time points indicated in Table 6-1.

The questionnaire must be administered by an Investigator or other individual that is suitably qualified by education or training. See APPENDIX 7 for a sample C-SSRS – Baseline/Screening version assessment and APPENDIX 8 for a sample post-dose C-SSRS (Since Last Visit Version) assessment.

If there is a positive result for suicidality on the C-SSRS after Screening (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.

6.1.8. Rescue Therapy

The clinical study site is equipped with emergency equipment and supplies that correspond with the level of risk associated with this study. In case of a medical emergency or an SAE requiring medical intervention, emergency equipment and supplies will be available and will include, but may not be limited to, stocked crash carts, oxygen source, suction pump, and defibrillator. Emergency medication (e.g., naloxone) or rescue medication required for advanced cardiac life support may be administered if deemed necessary by an Investigator or designee. If required, subjects will be transported to a hospital.

The Principal Investigator or designee will be on-site at the time of study drug administration until at least 4 hours postdose. When not available on-site, the Principal Investigator or designee will be on-call until the end of the study. While confined in the clinical site, subjects will be supervised by staff nurses and/or paramedics. Dedicated nurses and/or paramedics will be available to monitor AEs and perform safety measures. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded.

6.2. Pharmacokinetic Assessments

A total of 15 blood samples will be collected for PK assessments. The complete blood sampling schedule is presented in Table 6-7.

Table 6-7. Pharmacokinetic Blood Sampling Schedule

Sample No	Nominal Time[a] (hours)
01	0.00
02	0.25
03	0.50
04	1.00
05	1.50
06	2.00
07	2.50
08	3.00
09	4.00
10	6.00
11	8.00
12	10.00
13	12.00
14	24.00
15	48.00

a. Nominal times listed are relative to the time of study treatment administration.

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the subject or if judged necessary by the clinical staff, blood samples may be collected from a catheter, which will be placed in the vein of the subject.

The time of PK blood sample collection will be calculated relative to the time of treatment administration. The actual time of all PK blood draws will be recorded and reported for all subjects.

Windows for timed PK blood sample collections are presented in Table 6-8. PK samples collected outside of the pre-specified windows will be documented as protocol deviations. Since actual times are to be used for the PK analysis, deviations will be reflected in the analysis unless indicated otherwise upon review of the data.

Table 6-8. Acceptable Windows for Timed PK Blood Specimen Collection Procedures

Elapsed Time	Accepted Window
Predose	Within 60 minutes prior to study drug administration
> 0 hour to ≤ 30 minutes	± 1 minute
> 30 minutes to ≤ 4 hours	± 2 minutes
> 4 hours to ≤ 12 hours	± 5 minutes
> 12 hours to ≤ 24 hours	± 10 minutes
> 24 hours to ≤ 48 hours	± 2 hours

Mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine concentrations for PK assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using validated bioanalytical methods.

6.2.1. Pharmacokinetic Sample Processing, Storage and Shipping

Blood samples for PK determination will be processed, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

6.3. Pharmacodynamic Assessments

Pharmacodynamic assessments will be performed throughout the study as outlined in Table 6-1.

Prior to completing the computerized PD measures, all subjects will undergo a scripted training and practice regimen. Eligible subjects who appear to have difficulty differentiating between bipolar and unipolar visual analog scales (VAS) (e.g., making errors such as selecting a score of 50 to indicate the absence of a drug-effect on a unipolar scale) or difficulty distinguishing between "at this moment" and "next-day" measures will undergo additional 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. Subjects will be monitored carefully to ensure that they are completing the PD assessments appropriately; all reasonable attempts should be made to rouse subjects who fall asleep during testing cycles. If subjects cannot complete the PD assessments in a timely manner prior to the next required procedure or timepoint due to an AE, testing will be aborted.

6.3.1. 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. Pupil diameter will be measured as outlined in Table 6-1 and is further detailed in Table 6-9. Data from a series of frames will be used in the calculation, and the final display will show the weighted average and standard deviation (SD) of the pupil size. Measurements will be collected under mesopic lighting conditions. 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.

Table 6-9. 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 6-10.

Table 6-10. 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

6.3.2. Subjective Effects

Subjective measures will be evaluated as outlined in Table 6-1 and are further detailed in Table 6-11.

Table 6-11. 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; ARCI = Addiction Research Center Inventory; 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 6-12.

Table 6-12. 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

6.3.2.1. Visual Analogue Scales

All VAS will be scored on a 100-point scale, as shown in Table 6-13, and will be administered at the timepoints specified in Table 6-11. 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 6-13. 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	

Scale Interpretation	Include Predose	Type of Scale	Description	Question Text	Response Anchors
Other	Yes	Unipolar	Feeling Drunk	At this moment, I am feeling drunk	
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

6.3.2.2. 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.

6.3.2.3. 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 6-14. 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

6.3.2.4. 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 6-11.

The 49-item ARCI is a shortened version (49 true-false items) compiled by Martin et al.[7] from the 550-item ARCI originally developed by Haertzen.[8,9] 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 6-15.

Table 6-15. Addiction Research Center Inventory (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		

Question	Scale				
	A	PCAG	MBG	BG	LSD
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		
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

Question	Scale				
	A	PCAG	MBG	BG	LSD
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.

7. ADVERSE EVENTS DOCUMENTATION

7.1. Definitions

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.

A suspected adverse reaction is any AE for which there is a reasonable possibility the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study drug including comparator; it could be an abnormal clinical laboratory value as well as a significant shift from baseline within normal range which an Investigator considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of an Investigator)

7.2. Severity Assessment

All AEs will be graded per the current National Cancer Institute's Common Terminology Criteria for Adverse Events.

Every effort will be made to obtain an adequate evaluation of the severity.

7.3. Causality Assessment

An Investigator will determine the relationship of any AE to the study drug using the guidelines presented in Table 7-1.

Table 7-1. Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the investigational product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the investigational product. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the AE has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

Abbreviations: AE = adverse event; IP = investigational product; SAE = serious adverse event.

7.4. Adverse Event Monitoring

For the purposes of this study, the monitoring period for AEs extends from the pre-trial evaluation until collection of the last blood sample of the study. From screening to dosing of the study, AEs will be recorded as screening events or as part of the medical history, as applicable.

AEs occurring after initiation of study drug will be indicated as TEAEs in the clinical study report.

Subjects will be questioned on their health status at the beginning of each study period and before each departure from the clinical site. Open-ended questions will be asked.

During the study, all AEs spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded for all subjects and reported in the CRF.

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw from the study, they will be advised of the safety precautions to be taken.

Any AE which remains unresolved as of the last visit will require an evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence found, or is deemed mild and safely resolving.

In the case of AEs deemed related to the Investigational Product, every effort will be made to determine the final outcome.

It is an Investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or higher.

Concomitant medications will be coded using the World Health Organization drug dictionary (WHO-DDE March 2021 or later).

7.5. Reporting of Pregnancy

Pregnancy in a female study subject shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by an Investigator or delegate (for pregnancies occurring during the course of the study or immediately following the end of the study). Because of the possibility the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

Pregnancy that occurs within 90 days after study drug administration in a female partner of a male study subject shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by the clinical site that such pregnancy occurred during the course of the study or right after. Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the safety of the subject's female partner, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the clinical site to the Sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data

belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on an SAE Report Form.

7.6. Serious Adverse Event Reporting

The clinical site will notify any SAE to the Sponsor, without regard to causality, within 24 hours after becoming aware of its occurrence.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant info is available.

The notification should be directed to the following Sponsor representative:

Chad J Reissig, PhD
Supervisory Pharmacologist Center for Drug Evaluation and Research
Office of the Center Director, Controlled Substance Staff
U.S. Food and Drug Administration
Tel: 301-796-3434
chad.reissig@fda.hhs.gov

An SAE will be considered “unexpected” if the AE is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The clinical site will determine whether any serious unexpected related AE must be reported to the Institutional Review Board (IRB). If so, the event will be reported via fax or email within 15 calendar days of an Investigator or staff becoming aware of the event.

The Sponsor will determine whether the SAE must be reported in an expedited manner to the applicable regulatory agencies. If so, the Sponsor will report the event to those agencies and to all participating Investigators.

If reports of any new and unexpected AEs become available to the Sponsor during the clinical portion of this study (related or not to the present study), the Sponsor has to advise the clinical site, through its Clinical Investigator, of those events.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Analysis Populations

8.1.1. Randomized Population

The Randomized population will include all subjects who are randomized to receive either active drug (kratom) or placebo (6:2 active:placebo) in each cohort.

8.1.2. Safety Population

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

The number of subjects who were included, who discontinued, and who completed the study will be tabulated. The primary reasons for discontinuation will be provided.

8.1.3. Pharmacokinetic Population

In most cases, the decision about which subjects will be included in the PK analysis, is to be taken before the start of the sample analysis by the bioanalytical facility.

The PK population will be described in a statistical analysis plan (SAP). Generally, the PK population includes all the subjects who received kratom and have at least 1 postdose evaluable concentration value.

The PK population will be detailed in a SAP.

8.1.4. 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.

8.2. Demographic Data and Other Baseline Characteristics

Listings and descriptive summary statistics of demographic and baseline data will be presented.

8.3. Safety

The clinical laboratory tests, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), ECGs, physical examination findings, and C-SSRS will be used to perform the safety statistical analysis.

Descriptive statistics will be used to summarize AEs and safety results. The safety analysis will be fully detailed in the SAP.

8.4. Pharmacokinetics

The PK parameters C_{max}, T_{max}, AUC_{0-T}, $AUC_{0-\infty}$, $AUC_{T/\infty}$, λ_Z, and T_{half}, as well as the dose-normalized parameters C_{max}/D, AUC_{0-T}/D, and $AUC_{0-\infty}/D$ will be estimated for mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, and peciociliatine. Additional parameters may be calculated.

The PK analyses will be performed by non-compartmental analysis.

The PK analysis will be carried out according to Altasciences SOPs. Pharmacokinetic data handling and statistical analysis will be fully detailed in a SAP.

8.5. Pharmacodynamics

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.

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. 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 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}/TE_{min} between the 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.

The PD analysis will be fully detailed in a SAP.

8.6. Planned Interim Analyses

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.

8.7. 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.

9. REFERENCES

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10. APPENDIX 1: ETHICS

10.1. Institutional Review Board

This protocol and the ICF will be submitted to an IRB (or Independent Ethics Committee[IEC]) prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

10.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), the FDA GCP Code of Federal Regulations (CFR) Title 21 (part 56), the EU Clinical Trial Directive (EC) No. 2001/20/EC, the European regulation EU 536/2014 and the Tri-Council Policy Statement (Canada).

10.3. Subject Information and Consent

Before screening activities commence, each volunteer will be given a copy of the ICF to read, as well as a full explanation of the purpose of the study, the procedures to be carried out, and the potential AE(s). Once this essential information is provided to the volunteer and the Investigator or delegate in charge has the conviction the volunteer understands the implications of participating in the study, and if the volunteer chooses to continue the screening process, they will be requested to sign and date a properly executed ICF prior to enrollment. Subjects will be assured they may withdraw from the study at any time without jeopardizing their medical care or future study participation (for which they qualify).

Subjects will be given a signed copy of the ICF. If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained.

10.4. Subject Confidentiality

Investigators will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects personally identifiable information will be replaced with a unique subject identifier on all study documents . The key allowing for re-identification of the subjects will be maintained by the investigator and will not be released to the FDA. In compliance with Federal regulations/ICH GCP Guidelines, it is required an Investigator and Sponsor (FDA) permit authorized representatives of the company, of the regulatory agency(s), and IRB access to review the subject's original medical records for audit related activities including verification of study-related procedures and data. An Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the subject's confidentiality.

11. APPENDIX 2: DATA COLLECTION, RETENTION, AND MONITORING

11.1. Case Report Forms

The subject level data is entered by the site from the source document into a study specific 21 CFR Part 11 compliant electronic clinical database to accurately collect data for each subject included in a clinical trial. Screen failure data may be entered into the database at the discretion of the Sponsor, when included in the contracted scope of work.

11.2. Data Management and Processing

Data management develops documentation to define activities performed during the data management conduct of the study trial. The electronic data capture system is the tool used to conduct all data management data cleaning activities for monitoring, data review, and queries. Data management will use a combination of automated programmed edits and manual data review listings to issue queries for non-conforming or discrepant data. Data management activities are performed in accordance with the SOPs and study-specific data management documents.

Database locking is guided by the Data Management Locking Checklist based on the concept that all site activities are complete, data are considered clean and without errors, and CRF signoff by the Principal Investigator or delegate has been completed. User access is removed as part of the locking process.

Data from the clinical database will be output as SAS® datasets. All data will be included with the final report provided to the Sponsor.

11.3. Quality Control and Quality Assurance

Designated personnel from the quality assurance unit(s) will be responsible for maintaining quality assurance of the clinical, PK, statistical and bioanalytical facilities to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH Guideline E6 for GCP, applicable requirements as outlined in the FDA and Organization for Economic Co-operation and Development Principles of Good Laboratory Practice, and the *Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples* (EMA/INS/GCP/532137/2010).

Designated personnel from each corresponding operation unit will be responsible to maintain and assure the quality control of all data generated and documented in compliance with the protocol.

11.4. Record Retention

All essential documents and records will be maintained by the clinical site in accordance with, and for the period specified in the applicable regulatory requirement(s) (FDA CFR 312.57 [C]).

11.5. Monitoring of the Study

The sponsor or its representative may monitor the study in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct and/or virtual access, where possible, to source data/documents.

12. APPENDIX 3: ADMINISTRATIVE PROCEDURES

12.1. Liabilities

It is the Sponsor's responsibility to guarantee sufficient insurance coverage should any serious events or deaths result, either directly or indirectly, from the execution of the present protocol.

12.2. Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and the applicable regulatory requirements. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB for approval.

12.3. COVID-19 Response Plan

Regulatory authorities have recognized that the COVID-19 pandemic may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the IP(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the IP or adhering to protocol-mandated visits and laboratory/diagnostic testing. To accommodate these challenges and mitigate safety risks associated with COVID-19, protocol modifications may be required which include (and are not limited to):

- Conducting the study in multiple (smaller) subject groups;
- Altering the timing of study procedures and subject confinement;
- Modification of standard inclusion or exclusion criteria;

The exact mitigations will be documented in the study Risk Assessment and Mitigation Plan and will be discussed with the Sponsor before implementation.

Additional health checks including COVID-19 testing, body temperature monitoring, etc. may be performed during the trial, even if not planned within the protocol.

12.4. Statement of Investigator

The FDA 1572 form, Statement of Investigator [Title 21, CFR Part 312], will be signed by the Investigator, and will be kept on file.

12.5. Delegation of Investigator Duties

An Investigator will ensure all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

An Investigator will maintain a list of Sub-Investigator(s) and other appropriately-qualified persons to whom he/she delegates significant trial-related duties.

Should an Investigator delegate the supervision of the IP administration to a designated person, this individual must have the appropriate professional-legal qualifications and certifications. An Investigator should also ensure key staff personnel have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

12.6. Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the clinical site or an Investigator (or delegate) should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority(ies) when required.

13. APPENDIX 4: PROTOCOL REVIEW AND APPROVALS

ALTASCIENCES

TITLE: 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

I have carefully read this study protocol and agree it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with GCP and the applicable regulatory requirements.

Debra B. Kelsh M.D

Principal Investigator Name (Please Print)

Principal Investigator Signature
Altasciences Clinical Kansas Inc.

2023/07/24

Date (yyyy/mm/dd)

TITLE: 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

On behalf of the Sponsor, I am aware of, and agree to comply with, all of the procedures contained within this protocol.

_____ _____

Chad J. Reissig, PhD
Food and Drug Administration (FDA), USA

Date (yyyy/mm/dd)

14. APPENDIX 5: LIST OF ABBREVIATIONS

A	amphetamine
AE	adverse event
ALT	alanine aminotransferase
ARCI	Addiction Research Center Inventory
BG	Benzedrine Group
BMI	body mass index
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
LSD	lysergic acid diethylamide
MBG	morphine-benzedrine group
MDMA	3,4 methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MPC	minimum pupil diameter
MTD	Maximum Tolerated Dose
OAA/S	Observer's Assessment of Alertness/Sedation Scale
PCAG	pentobarbital–chlorpromazine–alcohol group
PCP	phencyclidine
PD	pharmacodynamic

pH	The Logarithm, On The Base 10, of The Reciprocal of The Hydrogen Ion Concentration
PK	pharmacokinetic
PT	Preferred Term
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Correction Formula
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog scale
WHO-DDE	World Health Organization Drug Dictionary Enhanced

15. APPENDIX 6: CLINICAL LABORATORY EVALUATIONS

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 low-density 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.

16. APPENDIX 7: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Lifetime: Time He/She Felt Most Suicidal	Past __ Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

	Most Severe	Most Severe
<u>Lifetime</u> - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
<u>Past X Months</u> - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

17. APPENDIX 8: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____