An Open-Label, Phase 1 Study of the Safety Pharmacokinetic Profile, and Preliminary Efficacy, of Organic Whole Psilocybin-Containing Mushrooms in Patients Suffering from PTSD

Protocol No:		**SRI-HRTT21**
Version:		**3**
Study Phase		**I**
Date		**25 July 2025**
Investigational Product		**Psilocybin**
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INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol SRI-HRTT21, Version 3, 25 July 2025

An Open-Label, Phase 1 Study of the Safety, Pharmacokinetic Profile, and Preliminary Efficacy, of Organic Whole Psilocybin-Containing Mushrooms in Patients Suffering from PTSD

This protocol will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices stated by the US Food and Drug Administration and the International Council of Harmonization, as well as applicable regulatory and/or Institutional Review Board requirements.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Signed by:
Sue Sisley
081096E7DEBE45D...

July 25, 2025

Investigator Name: Suzanne Sisley, M.D. | Date

Protocol Version History

Version	Date
Protocol Version 3	25 July 2025
Description of Modifications: The eligible population of participants was refined to include PTSD patients and not only treatment resistant PTSD patients. In addition, the primary endpoints were clarified to be more precise and the liver as well as the kidney function adverse events were added. Furthermore, the exploratory endpoints were clarified with the following psychiatric assessment and patient quality-of-life instruments added: Life Events Checklist for DSM-5 (LEC-5), PTSD Checklist for DSM-5 (PCL-5), Patient Health Questionnaire-9 (PHQ-9), NIH-HEALS, Profile of Mood States (POMS), Sheehan Disability Scale (SDS), 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), Alcohol Use Disorders Identification Test (AUDIT), Drug Use Disorders Identification Test (DUDIT). The following instruments were added in the synopsis to be aligned with the protocol: Generalized Anxiety Disorder Scale (GAD-7), Brief Pain Inventory (BPI), Watts Connectedness Scale (WCS), Mystical Experience Questionnaire (MEQ30) – Revised, Challenging Experience Questionnaire (CEQ). The following instruments were removed: Existential Distress Scale, Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16), Montgomery-Åsberg Depression Rating Scale (MADRS), EuroQoL-5 Dimensions-5 Levels questionnaire (EQ-5D-5L), Chronic-Pain Grade Scale (CGPS), Awe Experience Scale (AWE-S), Demoralization Scale (DS), Timeline Follow Back (TFLB), collectively. Exploratory objectives and endpoints regarding the impact of psilocybin mushrooms on sleep outcomes, heart rate and heart rate variability during sleep, daily activity and means changes in epigenetic markers of psychiatric and cardiovascular related genes were also added. Inclusion criteria were added such as acceptable renal and hepatic functioning. Participants will also be provided with a provided with a health tracking wearable device to monitor several variables such as total daily steps, sleep parameters as well as heart rate and blood pressure. The electronic daily diary to record their physical and mental health was removed. The product is administered as three 10 mg doses (30mg±10 %) instead of one 30mg dose (±5mg). All three units are administered concurrently during a single dosing session. Other modifications included: alignment of the synopsis with the protocol, refinement of the Schedule of Events (SOE), adding a second SOE table that provides more detailed information to guide the timing of protocol-mandated activities on Study Day 1, confirmation of protocol-required activities across all study visits including the need to return to the study site multiple times during the Screening Period, and consistency in language and timing for eligibility criteria, deletion of mention of life-threatening cancer from previous protocol version. In addition, timing of the post-eligibility confirmation one-to-one, group and ceremony activities as part of the Screening Period were established. And, the presence of a therapy dog, to provide emotional support also was incorporated. A slight refinement of the generalized statistical approach was added; details regarding the precise statistical methods to be employed will be incorporated in the planned Statistical Analysis Plan. Lastly, the roles and responsibilities of the independent Data Safety Monitoring Board (DSMB) were clarified, including that the specific elements of what the DSMB will do will be incorporated into the planned DSMB Charter. Other changes were editorial in nature and made throughout the document.	
Protocol Version 2.5	10 March 2025
Description of Modifications: The protocol was updated upon request from the FDA. The population was updated from terminal cancer or PTSD to only patients with treatment resistant PTSD. Inclusion criteria for anxiety and depression was added with values of 5 and above on General Anxiety Disorder Scale (GAD7) and Values of 7 and above on Montgomery-Åsberg Depression Rating Scale (MADRS)	

respectively. The inclusion criterion for pain was updated to CGPS 2 and above instead of previously 3 and above.	
Protocol Version 2.4	18 February 2025
Description of Modifications: The protocol was updated upon request from the FDA. The secondary and exploratory objectives were updated. The secondary objective is related to the characterization of the pharmacokinetic profile of psilocin. The exploratory objectives are the evaluation of the preliminary efficacy and quality of life. In addition, the population was updated from life-threatening illness to terminal cancer or PTSD.	
Protocol Version 2.3	20 January 2025
Description of Modifications: The protocol was updated upon request from the FDA. The ratio of participants-lead monitor was updated to 2:1 to not exceed 2 participants per 1 lead monitor. The protocol also specifies two safety monitoring session at 24-hours and 72-hours post-dose. The timing of safety and integration assessments have been aligned throughout the study synopsis, study protocol, and schedule of assessments. The clinical outcome assessments are reflecting the changes to establish the baseline. In addition, the protocol was modified when participants do not meet discharge criteria as well as to be escorted home by a trusted adult. Subjects who do not meet discharge criteria will receive prompt medical assessment prior to overnight observation and will be referred for additional medical treatment if indicated.	
Protocol Version 2.2	15 January 2025
Description of Modifications: The protocol was updated upon request from the FDA. The following changes were implemented in the protocol: locations and duties of all facilitators; the ratio participant/trained facilitator; subject-level stopping criteria; use of clinical outcome assessment; exclusion of subjects with QT≥450 msec; subjects observation until effects of dose administration have resolved; criteria for discharge; clarification of "psychotic attack" and other psychiatric adverse events assessment and determination if it constitutes study stopping criteria.	
Protocol Version 2.1	26 December 2024
Description of Modifications: The protocol specifies, that participants should not drive for at least 24 hours, instead of 8 hours mentioned previously, after drug administration. In addition, the term "effective form of birth control" has been changed to "highly effective form of birth control". Both changes have been implemented upon request from the FDA.	
Protocol Version 2	06 December 2024
Description of Modifications: The overall rationale for the changes implemented in the protocol amendment is to resolve the deficiencies upon request from the FDA mentioned in the FDA Clinical Hold letter received on April 4th, 2024. More specifically, the amendment seeks to provide a brief description of the compounding procedure used for preparation of "psilocybin mushrooms in chocolate" and necessary information on the botanical raw material. In addition, the design of the protocol has been updated to limit the dose to 30mg. Consequently, objective and endpoint to evaluate maximum tolerated dose (MTD) and the part 2 of the study were removed. The duration of the study was updated. To better reflect the initial objective of the Scottsdale Research Institute i.e. explore the safety (primary endpoint) of approximately 30 mg of psilocybin administered to patients, the comparator arm ("active placebo"), not necessary for such exploratory study, was removed. The protocol was also updated to outline subjects monitoring and to add subject and study stopping criteria as well as a Data and Safety Monitoring Board (DSMB). Finally, a plan to identify and manage subjects who present with significant symptoms of anxiety and depression was added. Exclusion criteria were also updated and a specific discharge criterion added.	
Protocol Version 1	02 February 2024

SYNOPSIS

Title:	**An Open-Label, Phase 1 Study of the Safety, Pharmacokinetic Profile, and Preliminary Efficacy, of Organic Whole Psilocybin-Containing Mushrooms in Patients Suffering from PTSD**
Brief Title:	**Safety and Preliminary Efficacy of Organic Whole Psilocybin-Containing Mushrooms to Treat Patients Suffering from PTSD**
Indication:	Post-Traumatic Stress Disorder (PTSD)
Protocol Number:	**SRI-HRTT21**
Phase:	I
Investigational Product:	**Whole Psilocybin-Containing Mushrooms (30 mg ±10 % of psilocybin)** milled and formulated into three solid chocolates, each delivering 10 mg of psilocybin. All three units are administered concurrently during a single dosing session.
Route of Administration	Oral
Sponsor:	Scottsdale Research Institute
Principal Investigator:	Suzanne Sisley, MD
Number of Participants:	24 treated participants
Number of Trial Sites:	1
Study Duration:	The overall duration of the patient enrollment, treatment and follow-up portions of the trial is expected to last 9 months. The duration of each patient's participation that completes the trial is expected to be between 3.5 and 4.0 months, depending on the length of time a patient is in the Screening phase (up to 4 weeks).

Primary Objective:	**Primary Endpoints**
• To evaluate the safety of psilocybin mushrooms.	• Number/Incidence of adverse events (AEs), and serious adverse events (SAEs) graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. ▪ Number/Incidence of AE's related to clinically significant ECG/cardiac function abnormalities ▪ Number/Incidence of AE's related to Heart Rate ▪ Tachycardia (*HR>100bpm)* ▪ Bradycardia (HR < 50 bpm) • Number/Incidence of AE's related to Blood Pressure ➢ Hypotension ➢ Hypertension • Number/Incidence of AE's related to Liver Function ➢ Liver function tests (i.e., liver enzymes) • Number/Incidence of AE's related to Kidney Function ➢ Renal function tests • Number/Incidence of Mental and Psychotic AE's

Secondary Objective:	**Secondary Endpoints**
• To characterize the pharmacokinetic profile of psilocin, the major active metabolite of psilocybin (using non-compartmental analysis).	• AUC_{0-t}, $AUC_{0-\infty}$ • Tmax • Cmax • $t_{½}$
Exploratory Objectives: • To evaluate the preliminary efficacy of psilocybin mushrooms. • To assess changes in quality-of-life (QoL) after taking psilocybin mushrooms. • To evaluate the impact of psilocybin mushrooms on objective sleep outcomes (sleep duration, sleep latency, sleep efficiency) via a health tracking wearable device. • To evaluate the impact of psilocybin mushrooms on heart rate and heart rate variability (HRV) during sleep via a health tracking, wearable device. • To evaluate the impact of psilocybin mushrooms on daily activity levels (i.e., steps) via a health tracking, wearable device. • To assess mean changes in epigenetic markers of psychiatric- and cardiovascular-related genes.	**Exploratory Endpoints:** • Generalized Anxiety Disorder 7 Item Scale (GAD-7) • Life Events Checklist for DSM-5 (LEC-5) • PTSD Checklist for DSM-5 (PCL-5) • Patient Health Questionnaire-9 (PHQ -9) • Healing Experience of All Life Stressors (NIH HEALS) • Brief Pain Inventory (BPI) • Columbia-Suicide Severity Rating Scale (C-SSRS) • Profile of Mood States (POMS) • Sheehan Disability Scale (SDS) • Watts Connectedness Scale (WCS) • Mystical Experience Questionnaire (MEQ30) – Revised • Challenging Experience Questionnaire (CEQ) • 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) • Alcohol Use Disorders Identification Test (AUDIT) • Drug Use Disorders Identification Test (DUDIT) • Nightly sleep duration, sleep latency, and sleep efficiency as measured via health tracking wearable device. • Heart rate and heart rate variability during sleep as measured via a health tracking wearable device. • Steps during daily activity as measured via a health tracking wearable device

Study Design:

This open-label Phase I trial will assess the safety, pharmacokinetics, and preliminary efficacy, of orally administered organic whole psilocybin-containing mushrooms among individuals with post-traumatic stress disorder (PTSD).

Up to 24 participants will be enrolled and treated with psilocybin mushrooms contained in a chocolate formulation. More detailed information on the required visit activities can be found in the SoE.

Prescreening:

Potential participants will provide verbal consent and be interviewed by phone to gauge their interest in and likelihood of qualifying for the trial.

Screening Period:

After signing an informed consent form (ICF), participants will enter a 2 to 4-week Screening Period to determine their eligibility for the trial. At the discretion of the Investigator, the Screening Period can be extended beyond 4-weeks if it is likely the patient will qualify for the trial.

Patients will undergo a physical examination and provide their relevant medical history, concomitant medications (including any drug use), have vital signs measured, provide urine samples for drug and alcohol screening and blood samples for clinical laboratory evaluations.

Females of childbearing potential will provide a urine sample for pregnancy testing. Lastly, all participants will have an electrocardiogram (ECG) performed.

If eligible, patients will be evaluated by appropriately trained assessors for multiple psychological factors, some of which will determine a participant's eligibility and establish baseline measures for comparison pre- and post-treatment.

Participants also will complete several self-assessment quality-of-life (QoL) and patient reported outcome instruments and will be provided with a health tracking wearable device to monitor several variables such as total daily steps, sleep parameters as well as heart rate and blood pressure.

Participants also will undergo individual preparatory training, wherein each participant will be assigned to trained facilitators to build trust and rapport and receive education on the potential effects of psilocybin mushrooms. Participants also will undergo a group education session conducted by trained facilitators to understand what to expect from the treatment and take part in a ceremony. Thus, participants may need to return to the study site up to three (3) times during the Screening Period.

Participants that do qualify for treatment will be asked to bring their pain medication with them to the study site on Study Day 1, the dosing day. They will be educated on how their pain will be managed and they will not be prohibited from being administered additional pain medication should their pain increase following administration of the investigational product.

Treatment Period:

Study Day 1: Eligible participants will be asked to return to the study site on Study Day 1. Participants will be instructed not to eat the morning of Study Day 1 and will not be permitted to eat for at least 4 hours following study drug administration. Thereafter, the study site staff will provide a light lunch. However, participants will be permitted water, if needed.

To ensure continued eligibility, participants will share their concomitant medications, have vital signs measured, provide urine samples for drug and alcohol screening and blood samples for clinical laboratory evaluations and for pharmacokinetic (PK) profiling. Females of childbearing potential will provide a urine sample for pregnancy testing and all participants will have an ECG performed and provide a saliva sample for epigenetic testing, as described in the SoE.

Prior to self-administering the study drug, participants will undergo a symbolic ceremony in which intentions are set and then will ingest the 3 doses of study drug, a whole dried organic hallucinogenic mushroom (RTT1121 also called JMF-01) which has been milled and formulated into3 solid chocolates. Each chocolate corresponds to 10 mg of psilocybin and participants will consume the 3 chocolates concurrently. Up to 8 participants will be treated at the same time.

All participants will be closely monitored for adverse events and for the onset and/or exacerbation of pain for at least 8 hours posttreatment. A maximum of two (2) participants will be assigned to an assistant trained facilitator in the room at all times, a 2:1 ratio. A Lead Therapist will monitor patients remotely (in a different room) with a maximum of 2 participants concurrently. Two additional facilitators will be on standby, if needed. If the Lead Therapist is not a physician, a physician will be on call and be able to respond to any medical emergency within 10 minutes. Group integration sessions with the trained facilitators will occur after the ceremony. In addition, a trained therapy dog will be available in the dosing room for additional

support, if requested by the participants.

Participants will continue to provide blood samples for PK assessments, for 8 hours, posttreatment (see PK Sampling in the SoE, Table 2) and complete any protocol-mandated QoL/PRO assessments. After the 8-hour PK sample is collected (unless there was reason to prematurely discontinue participation sooner), participants will be evaluated to determine if they can be discharged to home (accompanied by a trusted adult) or if they need to be monitored for an extended period and/or if additional medical intervention will be needed. Participants will leave with and continue to wear the health tracking device.

Study Day 2: Participants will return to the study site the next day, as close to 24 hours after the time of study drug administration on Study Day 1. Participants will have vital signs measured, share any changes in concomitant medications and complete an in-person group and an individual integration session. Participants also will be assessed for adverse events and be administered clinician rating scales for suicidal ideation/behavior, depression, and anxiety in addition to completing QOL and PRO instruments (see SOE).

Study Day 4: Approximately 72 hours after the time of study drug administration on Study Day 1, participants will undergo an individual virtual (via web meeting, phone, etc.) integration session and assessed for adverse events including mental health issues as well as for changes in concomitant medications.

Study Day 8: One week following Study Day 1, participants will return to the study site to undergo a physical exam, have vital signs measured, share any changes in concomitant medications and be assessed for adverse events. Participants also will be administered clinical rating scales and complete their QoL and PRO instruments. Participants also will provide blood and saliva samples for clinical laboratory evaluations and for epigenetic testing.

Study Day 30: At one month following the single administration of study drug on Study Day 1, participants will return to the study site for a Study Day 30 / End-of-Treatment (EOT) visit. Patients that prematurely discontinued participation on or after Study Day 1 will be encouraged to return to the study site for the EoT visit. At the EoT visit, participants will be assessed for adverse events and changes in concomitant medications, have vital signs measured, provide urine samples for drug and alcohol screening and blood samples for clinical laboratory evaluations as well as undergo clinical rating scale assessments and complete their QoL and PRO instruments.

Study Day 90: At three months following Study Day 1, participants will return to the research study center for the Long-Term Follow-up (LTFU) visit. At the LTFU visit, participants will be assessed for adverse events deemed to be 'possibly' or 'probably' related to the single dose of the investigational product administered on Day 1 and/or to monitor for resolution of any AEs that were not resolved by the EoT visit.

Participants also will have vital signs measured, provide urine samples for drug and alcohol testing as well as undergo and/or complete rating scale assessments and QoL and PRO instruments, respectively.

Participants also will return the health tracking wearable device, and the data collected during the trial from the health tracking wearable device will be downloaded to the trial database.

Upon completion of the 3-month LTFU visit and after the study site staff obtain all outstanding data, participants will have completed the study.

Diagnosis and Main Inclusion/Exclusion Criteria Eligibility:

Inclusion Criteria

1. Individuals ≥ 18 years of age
2. Have a diagnosis of Post-Traumatic Stress Disorder (PTSD) as defined:
   - Meet Diagnostic and Statistical Manual-5th edition (DSM-5) criteria for current PTSD with a duration of 6 months or longer as assessed by a study psychiatrist
   - Determination of at least one traumatic event as determined by the LEC-5

- A score of at least 33 on the PCL-5

3. Willing and able to provide signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
   - Willingly agreed to provide verbal consent to provide needed pre-screening information, including medical history, concomitant medications, etc., prior to signing the ICF.
4. Be willing to commit to self-administering the study drug, to completing the QoL and PRO instruments, and attending all study visits.
5. Participants must be able to evaluate their average pain on BPI (Brief Pain Inventory) over the past week.
6. Acceptable renal functioning as determined by no significant prior medical history and results of clinical laboratory evaluations done at Screening and on Day 1 (e.g., eGFR >45 (mL/min/1.73 m^2))
7. Acceptable hepatic functioning as determined by no significant prior medical history and results of clinical laboratory evaluations done at Screening and on Day 1 (e.g., liver enzymes ≤1.5x the upper limit of normal, 'ULN')
8. Agree to only use the psilocybin mushroom provided by site staff and not use any other psilocybin (or similar drug) in any form for at least 30 days prior to Study Day 1 and for 30 days following the single-dose study drug treatment.
9. Is willing to wear, sync daily, and charge twice weekly a provisioned health tracking wearable device every day during sleep and daily activity. If the participant already has the same or compatible device, they can use their own.
10. Agree to not use any psychoactive drugs, partake alcoholic beverages, self-administer ondansetron (or other selective serotonin reuptake inhibitors 'SSRIs', serotonin-norepinephrine reuptake inhibitors, 'SNRIs' and monoamine oxidase inhibits, 'MAOs'), cannabis, and/or any other non-routine PRN medications within 24 hours of Study Day 1. Exceptions include daily use of caffeine, nicotine, and opioid pain medication.
11. Be stable on any pre-study medications and/or psychotherapy regimen prior to study entry. Agree to inform physician(s)/clinician(s) providing current care about your participation in the study (or permit the research site study staff to do so). Agree to report any changes in medication or psychotherapy treatment regimen during the study, to study staff.
12. If female and of childbearing potential, the participant is eligible for the trial only with a negative urine pregnancy test during Screening and on Study Day 1. [If a result is uncertain (e.g., potential false positive), a serum human chorionic gonadotropin (hCG) test may be performed prior to the administration of the study drug.] Fertile females agree to use a highly effective form of birth control during the 30-day posttreatment period and must confirm that they have no intent to try to become pregnant or any need to breastfeed during this period.
    - Adequate birth control methods include intrauterine device (IUD), injected or implanted hormonal methods, oral hormones plus a barrier contraception, or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (ie, condom and diaphragm, condom or diaphragm and spermicide, oral hormonal contraceptives and spermicide or condom). Not of childbearing potential is defined as permanent sterilization or postmenopausal females.
13. Be proficient in reading and writing in English and able to effectively communicate with site staff.
14. Agree not to participate in any other interventional clinical trials during the study.

Exclusion Criteria

1. Currently or previously diagnosed with a psychotic, bipolar, or severe personality disorder.
2. Currently uncontrolled hypertension (>140/90 at Screening and >145/95 on Study Day 1).
3. History of recent seizure (within 3 months of Study Day 1).
4. History of stroke or transient ischemic attacks.
5. Preexisting history of valvulopathy or pulmonary hypertension.
6. A marked prolongation of QT interval (i.e., QT ≥450 msec) over a series of 3 ECGs performed within 5-6 minutes.
7. Currently uncontrolled diabetes. (HbA1c > 8.0%)
8. Potential for adverse drug-drug interactions such as the use of centrally-acting serotonergic agents within 24 hours prior to and for 72 hours following study drug administration on Study Day 1.
9. Significant suicide risk defined by (1) suicidal ideation as endorsed on items 4 or 5 on the Columbia Suicidal Severity Rating Scale (C-SSRS) within the last 6 months, at Screening, or at Baseline (Visit 1), or; (2) suicidal behaviors within the last 12 months as assessed by C-SSRS.
10. Patients with severe anxiety and depression measured as following - Patients with scores of 15 & above on Generalized Anxiety Disorder-7 (GAD-7) scale and Patients with scores of 20 & above on Patient Health Questionnaire-9 (PHQ -9).
11. Are pregnant or nursing or are women of childbearing potential who are not practicing a highly effective means of birth control.
12. Have any allergies or contraindication to psilocybin mushrooms.
13. Current users of psilocybin, LSD, DMT, Ayahuasca, Peyote, mescaline, and ketamine over the past 30 days will not qualify for the study unless the use of these agents is stopped for at least 30 days prior to Study Day 1 and the participant agrees to not use these (or similar) agents for 30 days after Study Day 1.
14. Are not able to attend face-to-face visits at the study site or plan to move out of the area prior to the 3-month LTFU visit.
15. Have any current problem, which in the opinion of the Investigator or Medical Monitor, might interfere with the individual's participation in the study or confound the assessment of safety and/or efficacy of the study drug.

Statistical Methods:

Descriptive statistics will assess the frequency of AEs or SAEs, laboratory parameters, and vital signs. Change in clinical and epigenetic outcomes will be measured from pre-treatment (baseline) to Study Day 7. Other exploratory endpoints will be assessed based upon changes from baseline for various quality-of-life (continuous) questionnaires, changes in sleep-related and other physiological measurements will be tracked using a wearable device. Plasma concentrations and PK parameters of psilocin will be summarized by descriptive statistics and graphically.

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1. LIST OF ABBREVIATIONS

Item		Description
5D-ASC		5-Dimensional Altered States of Consciousness Rating Scale
AE(s)		Adverse events
ALP		Alkaline phosphatase
ALT / SGPT		Alanine aminotransferase / Serum glutamic pyruvic transaminase
AST / SGOT		Aspartate aminotransferase / Serum glutamic-oxaloacetic transaminase
AUC_{0-t}		Area under the concentration-time curve (AUC) from time zero (i.e., dosing time) to the time of the last quantifiable concentration.
$AUC_{0-\infty}$		The AUC from time zero extrapolated to infinity using linear regression.
AUDIT		Alcohol Use Disorders Identification Test
BP		Blood pressure
BPI		Brief Pain Inventory
bpm		Beats per minute
BUN		Blood urea nitrogen
°C		Centigrade (temperature)
CBF		Cerebral blood flow
CEQ		Challenging Experience Questionnaire
C_{max}		Maximum observed concentration
C-SSRS		Columbia Suicide Severity Rating Scale
DEA		Drug Enforcement Administration
DMN		Default mode network
DMT		N,N-Dimethyltryptamine
DSM-5		Diagnostic and Statistical Manual of Mental Disorders – 5th edition
DSMB		Data Safety Monitoring Board
DUDIT		Drug Use Disorders Identification Test
eCRF		Electronic case report form
ECG		Electrocardiogram
EDC		Electronic data capture
EoT		End of Treatment (visit)
°F		Fahrenheit (temperature)
FDA		Food and Drug Administration
fMRI		Functional magnetic resonance imaging
GCP		Good Clinical Practice
GAD-7		Genaralized Anxiety Disorder 7-Item Scale
GGT		Gamma-glutamyl transferase
hCG		Human chorionic gonadotropin

HIPAA		Health Insurance Portability and Accountability Act
HR		Heart rate
HRV		Heart rate variability
ICF		Informed Consent Form
IRB		Institutional Review Board
IUD		Intrauterine device
LDH		Lactate Dehydrogenase
LEC-5		Life Events Checklist for DSM-5
LSD		Lysergic acid diethylamide
LTFU		Long-term follow-up visit (~90 days / 3 months)
m^2		Meter squared
MAO		Monoamine oxidase inhibitors
MCH		Mean corpuscular hemoglobin
MCV		Mean corpuscular volume
MEQ30		Mystical Experience Questionnaire – Revised
mg		Milligram
min(s)		Minute(s)
mL		Milliliter
NCI CTCAE		National Cancer Institute's Common Terminology Criteria for Adverse Events
NIH HEALS		Healing Experience of All Life Stressors
PCL-5		PTSD Checklist for DSM-5
pH		Concentration of hydrogen
PHQ-9		Patient Health Questionnaire-9
pK		Pharmacokinetic
POMS		Profile of Mood States
PRN		*Pro re nata* (as needed)
PRO		Patient reported outcome
PTSD		Post-traumatic stress disorder
QoL		Quality-of-Life
QT (interval)		ECG measured: Q-wave to T-wave time duration
RBC		Red blood cell
RR		Respiration rate
SAE(s)		Serious Adverse Events
SDS		Sheehan Disability Scale
SoE		Schedule of Events
SpO_2		Peripheral capillary oxygen saturation
SSRI		Selective serotonin reuptake inhibitor
TBI		Traumatic brain injury
TEAE		Treatment emergent adverse event

T_{max}		Time to reach maximum observed concentration during a dosing interval
$t_{½}$		Time to reach one-half of the original, maximum observed concentration
UGT		UDP-glucuronosyltransferase
ULN		Upper limit of normal range
WBC		White blood cell
WCS		Watts Connectedness Scale

2.BACKROUND AND STUDY RATIONALE

2.1. Background

This Phase I trial is designed to assess the anecdotal reports of individuals successfully using psilocybin mushrooms to manage a variety of symptoms. Indeed, there is literature that suggests that many people are using psilocybin mushrooms to help control their anxiety, depression and PTSD symptoms, in a safe and effective manner (Raison 2022).

Psilocybin is becoming more available through decriminalization efforts (e.g., in Oakland, and Santa Cruz, California and in Denver, Colorado). However, the only clinical trials that have been conducted with high dosages of psilocybin use synthetic psilocybin. At present, there are no published data from controlled trials on the safety and tolerability of whole organic psilocybin mushrooms used to treat individuals with PTSD.

2.2. Study Purpose

This open-label, Phase I study, will evaluate the safety, pharmacokinetics and preliminary efficacy of whole organic psilocybin mushrooms. This will be the first clinical trial testing the therapeutic potential of organic whole psilocybin mushrooms for patients with PTSD and will help determine the potential risks and benefits of using psilocybin as a treatment for PTSD. The results garnered from this trial can be used to inform the design of larger randomized controlled clinical trials.

The results also will provide physicians, patients, scientists, and regulators with critical knowledge regarding whether organic whole psilocybin mushrooms may have benefits in treating commonplace comorbidities of PTSD such as pain, anxiety and depression for individuals with PTSD, and the impact of this popular but untested regimen on clinical outcomes.

Individuals with PTSD that are to be included in this study will have satisfied the Diagnostic and Statistical Manual-5th edition (DSM-5) criteria for current PTSD with a duration of 6 months or longer, as assessed by a study psychiatrist.

2.3. Supporting Information

2.3.1 Condition

Posttraumatic stress disorder (PTSD) is a debilitating, chronic disorder and efficacy rates associated with current PTSD treatments are underwhelming. Although there is no published data on psilocybin use for treating PTSD, the building evidence of the utility of psilocybin on conditions that often co-occur with PTSD, such as depression and anxiety, indicates the potential beneficial impact of the psilocybin augmented PTSD treatment.

Despite the lack of formal research data, the anecdotal evidence suggests psilocybin may be a promising treatment for PTSD. While the exact pathophysiology of PTSD is not fully elucidated, it is thought that a dysregulated fear response is one facet of the disease state (Abdallah 2019). Kometer et al. discovered that psilocybin enhanced positive mood, potentially reducing negative thoughts in PTSD patients that experience comorbid depression (Kometer, 2012).

Functional magnetic resonance imaging (fMRI) studies of participants' brains after dosing psilocybin show decreased cerebral blood flow (CBF) and decreased reactivity in the amygdala (Carhart-Harris, 2017; Tylš, 2014). Abdallah et al. also noted that the default mode network (DMN) is hypoactive and weakly interconnected in those with PTSD. A hypoactive DMN is associated with symptoms such as avoidance, dissociation, and intrusive thoughts which are observed in PTSD (Adballah, 2019). Carhart-Harris et al. published an fMRI study in 2012 that performed blood-oxygen level-dependent fMRI on 15 participants injected with either 2mg psilocybin in 10mL saline or a 10mL saline placebo. The results indicated that psilocybin induced lower levels of CBF in the DMN, among several other regions of the brain (Carhart-Harris, 2012).

Recent clinical studies suggest that psilocybin mushrooms may be an effective treatment option in promoting better outcomes with people in reducing symptoms associated with both depression and anxiety as well as the psychological stress faced by individuals faced with life-threatening illness (Simonsson, 2023; Goodwin, 2022; von Rotz, 2022; Ross, 2021; Schimmel, 2021; Yu, 2021; Carhart-Harris, 2018; Carhart-Harris, 2016; Griffiths 2016; Ross 2016). In a meta-analysis of the effects of psychedelics (including psilocybin on symptoms of life-threatening illness, PTSD, and autism) authors report that there is an 80% probability that individuals that were given psychedelics had better outcomes than those given a placebo (Luoma 2020). These effects were found to be long-term.

A second meta-analysis of the effects of psilocybin on depression found that 2 doses rather than 1 dose of psilocybin were shown to have stronger effects on reducing depression and that these effects were long-lasting, for up to 6-months (Yu 2022). The safety of psilocybin also was assessed and the authors report that while systolic and diastolic blood pressure increased with psilocybin use, the cardiovascular profile was safe.

Furthermore, these authors also conducted a meta-analysis on the effects of psilocybin on anxiety and reported that psilocybin reduced end-of-life anxiety and that this effect persisted for 6 months after a single treatment session (Yu 2021). There were no differences in serious adverse events between the psilocybin and placebo treatment groups.

Lastly, a recent review of the literature examined the effect of psilocybin on depressive symptoms and described an optimal therapeutic range of 30-35 mg was associated with improved symptomatology (Li 2022).

Studies of psilocybin use in naturalistic settings are important as many individuals that experience anxiety and depression use organic, whole, psilocybin mushrooms in the real world to relieve their symptoms. In the Psychedelic and Wellness study, individuals were given a survey to examine the influence of psychedelics on well-being (Raison 2022). Anonymous retrospective assessments of the effects of psilocybin on depression, anxiety, and well-being were queried in 2,510 adults ranging in age from 18 to 86 years. Over 50% of individuals preferred psilocybin to ameliorate symptoms. Individuals that used psychedelics reported experiencing decreases in anxiety and depression and increases in well-being. However, 13% of individuals described that using psychedelics were harmful including accompanying drug and alcohol use as well as suicidal ideation.

2.3.2 Psilocybin as a Potential Treatment for patients with PTSD

Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) is a substituted indolylalkylamine and belongs to the group of hallucinogenic tryptamines. Psilocybin was first isolated in a mushroom species (*Psilocybe mexicana)* and also has been synthesized.

Pharmacokinetics

Psilocybin is a prodrug that is metabolized to psilocin. Psilocin, due to its lipophilicity, is able to cross the blood-brain barrier and produce neurological effects. After ingestion, psilocybin is rapidly converted to psilocin in the stomach, intestines, blood, and kidneys. Studies suggest fasting for 2-4 hours before taking psilocybin.

Psilocybin has about 50% bioavailability and is detectable in plasma within 20-40 minutes. Psilocin is detectable in plasma after 30 minutes and has linear pharmacokinetics. The half-life of psilocin is around 108 minutes, and its effects last 4-6 hours. Psilocin is mainly metabolized by the liver through UGT 1A10 and UGT 1A9 enzymes into psilocin-O-glucuronide and excreted through urine and feces, with complete excretion within 24 hours.

Pharmacodynamics and Psychedelic Effects

Psilocin, the primary active metabolite of psilocybin, is highly lipophilic and readily crosses the blood brain barrier. Psilocin has a high affinity for the 5-HT2A serotonin receptor, which is responsible for its hallucinogenic effects, and that of many psychedelic drugs. Molecules that activate this receptor are known to stimulate the production of the brain-derived neurotrophic factor (BDNF) and enhance the efficiency of signaling between neurons.

The acute effects of psilocybin on brain activity have been graphically demonstrated in 2 functional magnetic resonance imaging studies, which showed how networks of regions that usually operate independently become more functionally interconnected, while connectivity within the 'default mode network'— a network associated with mind-wandering and the sense of self—is disrupted (Carhart-Harris 2012; Carhart-Harris 2017). The default mode network is overactive in people who are prone to depression and is thought to be responsible for the excessive self-referential thought and rumination that characterizes depression. Therefore, alteration of this network, as shown by acute decreases in cerebral blood flow in key default mode brain regions, may guide the understanding of the antidepressant effects of psychedelics like psilocybin.

2.4. Rationale for Dose Selection

For this study, 30 mg (±10 %) of psilocybin from dried mushrooms and administered as three 10 mg doses in a chocolate formulation, has been chosen. The available literature suggests that this dosage is effective and generally well-tolerated, with a favorable safety profile in various indications. Recent findings regarding psilocybin's ability to alleviate PTSD and traumatic brain injury (TBI) symptoms are encouraging at this dose (Miller et al, 2024, Zarestsky et al, 2024).

Higher doses (20-35mg) could be associated with an increased risk of psychological adverse events, such as fear, paranoid thoughts, and ideas of reference (MacCallum et al., 2022;

Goodwin, 2022; Ross, 2021; von Rotz, 2023). Straumann et al. (2024) examined the safety profile of psilocybin in healthy individuals by pooling data from three randomized crossover studies involving 85 participants and 113 single-dose administrations of psilocybin (ranging from 15 mg to 30 mg). The findings indicate that psilocybin is generally safe in terms of acute psychological and physical harm. At all doses, psilocybin induced higher "good drug effects" than "bad drug effects." Only the 25 mg and 30 mg dosages were found to increase anxiety. Psilocybin moderately elevated autonomic effects. Tachycardia (heart rate > 100 beats/min) was observed in 7% of all psilocybin administrations. Body temperature exceeded 38°C in 7%, 9%, 17%, and 32% of participants with the 15 mg, 20 mg, 25 mg, and 30 mg doses, respectively. No significant changes were observed in kidney and liver function parameters. No serious adverse reactions were reported. The study concluded that a single administration of 30 mg of psilocybin is safe in terms of acute psychological and physical harm in a controlled research setting.

3.OBJECTIVES

3.1. Primary Objective

- To evaluate the safety of psilocybin mushrooms.

3.2. Secondary Objective

- To characterize the pharmacokinetic profile of psilocin, the major active metabolite of psilocybin (using non-compartmental analysis).

3.3. Exploratory Objectives

- To evaluate the preliminary efficacy of psilocybin mushrooms.
- To assess changes in quality of life after taking psilocybin mushrooms.
- To evaluate the impact of psilocybin mushrooms on objective sleep outcomes (sleep duration, sleep latency, sleep efficiency) via a health tracking wearable device.
- To evaluate the impact of psilocybin mushrooms on heart rate and heart rate variability (HRV) during sleep via a health tracking wearable device.
- To evaluate the impact of psilocybin mushrooms on daily activity levels (i.e., steps) via a health tracking wearable device.
- To evaluate mean changes in epigenetic markers of psychiatric- and cardiovascular-related genes.

4. INVESTIGATIONAL PLAN

4.1. Study Design

This open-label Phase I study will assess the safety, pharmacokinetics, and preliminary efficacy, of orally administered organic whole psilocybin-containing mushrooms in patients suffering from PTSD. Up to 24 participants will be enrolled and treated with psilocybin mushrooms contained in a chocolate formulation.

A description of the key activities to be done at each study visits is presented below; more detailed information on the required activities, including examinations, tests, procedures and assessments can be found in Section 6 and in the Scheduled of Events (SOE).

Prescreening:

Potential participants that are made aware of this trial from an Institutional Review Board's (IRB) approved materials and/or by clinicians will undergo a prescreening interview by phone (or via a web meeting application) to gauge their interest in participating in this trial as well as to review their relevant medical history.

- Information on the participant's medical history only will be collected after the individual provides verbal consent and it is explained that if he/she decides not to participate, all their personally identifiable information will be deleted (to the extent reasonably practicable), including their medical information.

Screening Period:

After signing an informed consent form (ICF), participants will enter a 2 to 4-week Screening Period to determine their eligibility for the trial. At the discretion of the Investigator, the Screening Period can be extended beyond 4 weeks if it is likely the patient will qualify for the trial.

Patients will undergo a targeted physical examination and provide more details about their relevant medical history, concomitant medications (including any psychedelic and/or other drug use), have their vital signs and blood pressure measured, provide urine samples for drug and alcohol screening and blood samples for clinical laboratory evaluations.

Females of childbearing potential will provide a urine sample for pregnancy testing. Lastly, all participants will have an electrocardiogram (ECG) performed.

Unless a finding is made that excludes a participant from the trial, they will be evaluated by appropriately trained assessors for multiple psychological factors and assessments (including the LEC-5 and the PCL-5), some of which will determine the participant's eligibility as well as establish baseline measures for comparison pre- and post-treatment of exploratory objectives.

Participants will be required to complete several self-assessment quality-of-life (QoL) and patient reported outcome (PRO) instruments. They also will be provided with a health tracking wearable device to monitor several variables such as total daily steps, sleep parameters as well as heart rate and blood pressure. [If a participant already owns a suitable health tracking wearable device, they may use their own instead of the device provided for the trial.]

Participants that qualify for treatment will undergo individual preparatory training wherein each participant will be assigned to trained facilitators to build trust and rapport and receive education on the potential effects of psilocybin mushrooms. A Lead Therapist also will conduct a group education session regarding the treatment and take part in a ceremony following the individual preparation session.

Participants will be asked to bring their pain medication to the study site on Study Day 1, the dosing day. They will be educated on how the pain will be managed and they will not be prohibited from being administered additional pain medication should their pain increase following administration of the study drug. Patients who use opioid analgesics will be instructed to maintain their usual regimen.

- To the extent possible, input will be obtained from the participant's regular clinical providers on appropriate pain management for the participant during the trial, particularly in the case of analgesics associated with adverse reactions of concern with psilocybin (e.g., QTc prolongation with methadone).

During the screening period if a participant is found to have serious anxiety attack or another psychotic episode then the participant is referred to the relevant psychiatrist or responsible physician for follow up and treatment. Additionally, if the participant develops any medical emergency he/she will be managed as per the procedures described in detail under section 9.5.

Treatment Period:

Study Day 1: Eligible participants will be asked to return to the study site on Study Day 1. Participants will be instructed not to eat the morning of Study Day 1 and will remain fasting (i.e., not be permitted to eat) for at least 4 hours following study drug administration (see Section 7.5). Thereafter, the study site staff will provide a meal. However, participants will be permitted water, if needed.

To ensure continued eligibility prior to the administration of the study drug, participants will undergo protocol-mandated tests, procedures and assessments including reviewing their concomitant medications, have vital signs and blood pressure measured, provide urine samples for drug and alcohol screening. Participants also will have blood samples collected for clinical laboratory evaluations, but the results will not be needed to confirm continued eligibility for study drug administration. Females of childbearing potential also will need to provide a urine sample for pregnancy testing (with a negative result prior to dosing) and all participants also will have an ECG performed and will provide a saliva sample for epigenetic testing. Certain clinical assessments also will be required to be done, including both clinician rating scales and patient QoL and PRO instruments.

Prior to self-administering the study drug, participants will undergo a symbolic ceremony directed by the Lead Therapist in which intentions are set and then they will ingest 3 doses of the psilocybin containing chocolate preparation. The investigational product is a whole dried organic hallucinogenic mushroom (RTT1121 also called JMF-01) which has been milled and formulated into 3 solid chocolates. Each chocolate corresponds to 10 mg of psilocybin. Group integration sessions with the trained facilitators will occur after the ceremony.

- Up to a maximum of 8 participants will be treated at the same time. During dosing, there will be two qualified staff (a designated therapist acting as the assistant monitor and a lead monitor) monitoring the participant at all times (the designated/assistant therapist in the session room and the lead monitor, a physician or licensed nurse practitioner, via live remote monitoring on site in a separate room).
- For each pair (i.e., 2) of participants, there will be at least one assistant trained facilitator in the session room directly assigned (a 2:1 ratio).
- The Lead Therapist serving as the lead monitor will monitor patients remotely (in a different room) with a maximum of 2 participants concurrently.
- The lead monitor must be a licensed healthcare provider with professional training and

clinical experience in psychotherapy and be actively licensed to practice independently in the state of the study site location. Acceptable professional credentials for the lead monitor/therapist may be one of the following:

  - Clinical or counseling psychologist (PhD or PsyD)
  - Psychiatrist or other physician (MD or DO)
  - Master of Social Work (MSW)
  - Licensed Clinical Professional Counselor (LCPC)
  - Licensed Marriage and Family Therapist (LMFT)
  - Psychiatric Nurse Practitioner (Psychiatric NP)

- If the lead monitor is not a physician, a licensed, on-call, physician must be available and able to reach the clinical site within 10 minutes of a medical emergency.

- The designated/assistant monitor must have a bachelor's degree and at least one year of clinical experience in a licensed mental healthcare setting.

  In addition, two back-up facilitators will be on standby to be available, if needed, to assist with any issues that may arise.

  - [This participant monitoring approach is consistent with the recommendations contained in the FDA Draft Guidance titled, Psychedelic Drugs: Considerations for Clinical Investigations (June 2023).]
  - A trained therapy dog also will be available in the dosing room for additional support, if requested by the participant.

During Study Day 1 (and at any other in-person study related visit at the study site) if a participant develops a psychiatric emergency (as diagnosed by the physician), verbal de-escalation, education and support will be used to maintain the safety of the participant and the facilitators. Participants will not be allowed to leave the premises until the drug effects have worn off. If the patient is not de-escalated then the patient would be transferred to an in-patient center for better care. Additionally, any medical emergencies will be dealt with as per the procedures described in Section 9.5.

- Additionally, if the participant reports an increase in pain, they will be treated with their then current pain medication. If needed, additional pain medication may be administered by the Investigator.

Following the administration of the 3 doses of study drug, participants will be instructed to lie down wearing eyeshades and listen to a preselected music playlist via headphones and speakers. The participants will be required to remain at the study site for at least 8 hours following the time of study drug administration. During this period, participants will be closely monitored for adverse events, including the onset and/or exacerbation of pain.

Participants also will continue to provide blood samples for PK testing (see Section 8.2 and the SoE). After the 4-hour PK blood sample is collected, participants will be provided with a meal.

After the 8-hour post-dose PK sample is obtained, a participant may be discharged from the study site provided all protocol-mandated examinations, procedures and assessments (described below) have been completed, and the participant is deemed to be in an adequate physical and mental state of being.

Prior to discharge on Study Day 1, participants will need to complete (and/or be administered) a set of clinical rating scale, QoL and PRO instruments including the Profile of Mood States (POMS), the revised Mystical Experience Questionnaire (MEQ30), the Challenging Experience Questionnaire (CEQ) and the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC). Participants may be discharged, when in the opinion of the investigator, the acute effects of psilocybin are resolved. Participants may be discharged only if the posttreatment POMS score is at below 125% of the baseline score. If the POMS score is greater than the 125% threshold the participant will remain at the study site and provided with meals and lodging. Participants that are discharged must be accompanied by an adult.

Study Day 2: participants will return to the study site the next day as close as reasonably possible to 24 hours after the time of the study drug administration on Study Day 1. Participants will have vital signs measured, share any changes in concomitant medications and will complete an in-person group and an individual integration session. Participants also will be assessed for adverse events and be administered clinician rating scales for suicidal ideation/behavior, depression, and anxiety in addition to completing QOL and PRO instruments.

Study Day 4: Approximately 72 hours after the time of study drug administration on Study Day 1, participants will undergo an individual, virtual (via web meeting, phone, etc.) integration session, and be assessed for adverse events including mental health issues as well as for changes in concomitant medications and clinician rating scales and patient QoL/PRO instruments will be completed.

Study Day 8: One week following Study Day 1, participants will return to the study site to undergo a physical exam, have vital signs measured, and share any changes in concomitant medications as well to be assessed for adverse events. Participants also will be administered clinical rating scales and complete their QoL and PRO instruments. Participants will provide blood and saliva samples for clinical laboratory evaluations and for epigenetic testing.

Study Day 30: Unless discontinued from participation earlier, at one month following Study Day 1, participants will return to the study site for an End-of-Treatment (EOT) visit. Patients that prematurely discontinued participation on, or after being treated on Study Day 1 will be encouraged to return to the study site for the EoT visit as soon as possible and need not wait till Study Day 30).

At the EoT visit, participants will be assessed for adverse events and changes in concomitant medications, have vital signs measured, provide urine samples for drug and alcohol screening and blood samples for clinical laboratory evaluations as well as undergo clinical rating scale assessments and complete their QoL and PRO instruments.

Study Day 90: Three months following Study Day 1, participants will return to the research study center for the Long-Term Follow-up (LTFU) visit. At the LTFU visit, participants will be assessed for adverse events deemed to be 'possibly' or 'probably' related to the single dose of the investigational product administered on Study Day 1 and/or to assess any AEs that were not resolved by the EoT visit.

Participants also will have vital signs measured, provide urine samples for drug and alcohol testing as well as undergo and/or complete rating scale assessments and QoL and PRO

instruments, respectively.

Participants also will return the health tracking wearable device and the data collected will be downloaded to the trial database.

Upon completion of the 3-month LTFU visit and after the study site staff obtain all outstanding data, participants will have completed the study.

4.2. Premature Discontinuation

Participants can elect to prematurely discontinue their involvement in this trial at any time and for any reason (see Section 6.3 for more detailed information regarding a participant's rights and responsibilities). If a decision to prematurely discontinue participation is made, the Investigator (or designee) may ask the individual to continue to be followed for safety and indicate that they will not have to undergo any other tests, examinations or procedures. However, the participant will not be coerced into continuing to be involved in the trial, even in a less demanding manner.

Otherwise, the participant can terminate their involvement in the trial, without prejudice, and not affect their continued medical care.

Participants also may be prematurely discontinued from the trial by the Investigator if it is determined that continued involvement could adversely affect their health and/or wellbeing. Other reasons for premature discontinuation include adverse effects, a participant's lack of adherence to the requirements of the protocol or other issues that, in the opinion of the Investigator could confound the assessments of safety (and/or preliminary efficacy) of the investigational product.

4.3. Study Duration

The overall duration of the patient enrollment, treatment and follow-up phase of the trial is expected to last 9 months.

The duration of an individual's participation, that completes the trial (Screening through the 3-month posttreatment LTFU visit) will be between 3.5 to 4.0 months depending on the length of time a participant is in the Screening Period (up to 4 weeks). [In rare cases, a participant's total duration of involvement could extend beyond 4.0 months if the Screening Period is extended and/or if it is deemed necessary to continue to monitor an adverse event that did not resolve prior to the date of the 3-month posttreatment LTFU visit.]

4.4. Study Endpoints

4.4.1 Primary Endpoints

Primary endpoints will be assessed using descriptive statistics. The statistical approaches are described Section 13.3 and will be detailed in the Statistical Analysis Plan (SAP) that will be developed and finalized before any analyses are undertaken.

- Number/Incidence of adverse events (AEs), and serious adverse events (SAEs) graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
  - Number/Incidence of AE's related to clinically significant ECG/cardiac abnormalities

  - Number/Incidence of AE's related to Heart Rate
    - Tachycardia (HR>100 bpm)
    - Bradycardia (HR < 50 bpm)
  - Number/Incidence of AE's related to Blood Pressure
    - Hypotension
    - Hypertension
  - Number/Incidence of AE's related to Liver Function
    - Liver function tests
  - Number/Incidence of AE's related to Kidney Function
    - Renal function tests
- Number/Incidence of Mental and Psychotic AE's

4.4.2 Secondary Endpoints

Pharmacokinetic parameters will be estimated using standard methods; the statistical approaches are described in Section 13.4 and will be detailed in the Statistical Analysis Plan (SAP) that will be developed and finalized before any analyses are undertaken.

- PK parameters of psilocin including:
  - AUC_{0-t}
  - $AUC_{0-\infty}$
  - T_{max}
  - C_{max}
  - $t_{½}$

4.4.3 Exploratory Endpoints

Exploratory endpoints will be driven by a fundamental analysis of mean changes in clinician rating scales and patient QoL and PRO instruments compared from baseline to one or more visit timepoints. Mean changes in epigenetic markers also will be assessed. In addition, data captured by the health tracking wearable device will be assessed. For all exploratory endpoints, appropriate statistical methods will be employed as described, more generally in Section 13.5. A formal outline of the statistical methods to be employed will be detailed in the SAP.

- At Screening, participants will confirm that they have had a traumatic event, captured in the LEC-5 and that they have a minimum score of at least 33 as determined the PCL-5, respectively.
- Mean changes from baseline to various study visit timepoints (e.g., Study Day 7) will be calculated for the following instruments:
  - General Anxiety Disorder 7 Item Scale (GAD-7)
  - Patient Health Questionnaire-9 (PHQ -9)
  - Healing Experience of All Life Stressors (NIH HEALS)
  - Brief Pain Inventory (BPI)
  - Columbia-Suicide Severity Rating Scale (C-SSRS)

- Profile of Mood States (POMS)
- Sheehan Disability Scale (SDS)
- Watts Connectedness Scale (WCS)
- Mystical Experience Questionnaire-revised (MEQ30)
- Challenging Experience Questionnaire (CEQ)
- 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)
- Alcohol Use Disorders Identification Test (AUDIT)
- Drug Use Disorders Identification Test (DUDIT)

- Mean changes in epigenetic markers from baseline to various timepoints will be calculated for psychiatric and cardiovascular genes.
- Data collected by a health tracking wearable device such as nightly sleep duration, sleep latency, sleep efficiency, heart rate and heart rate variability during sleep, and daily steps will be calculated.

5. PARTICIPANT ELIGIBILITY, ENROLLMENT AND WITHDRAWAL

5.1. Description of the Population

A total of up to 24 participants, ≥18 years of age and diagnosed with PTSD will be enrolled and treated in this Phase I trial. Participants may be men or women and of any race or ethnicity.

In order to qualify to participate, individuals must satisfy all the Inclusion Criteria and none of the Exclusion Criteria.

5.1.1 Inclusion Criteria

1. Individuals ≥ 18 years of age
2. Have a diagnosis of Post-Traumatic Stress Disorder (PTSD) as defined:
   - Meet Diagnostic and Statistical Manual-5th edition (DSM-5) criteria for current PTSD with a duration of 6 months or longer as assessed by a study psychiatrist.
   - Determination of at least one traumatic event as determined by the LEC-5
   - A score of at least 33 on the PCL-5
3. Willing and able to provide signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
   - Willingly agreed to provide verbal consent to provide needed pre-screening information, including medical history, concomitant medications, etc., prior to signing the ICF.
4. Be willing to commit to self-administering the study drug, to completing the QoL and PRO instruments, and attending all study visits.
5. Participants must be able to evaluate their average pain on the BPI (Brief Pain Inventory) over the past week.
6. Acceptable renal functioning as determined by no significant prior medical history and results of clinical laboratory evaluations done at Screening and on Day 1 (e.g., eGFR >45 (mL/min/1.73 m^2))

7. Acceptable hepatic functioning as determined by no significant prior medical history and results of clinical laboratory evaluations done at Screening and on Day 1 (e.g., liver enzymes ≤1.5x the upper limit of normal, 'ULN')
8. Agree to only use the psilocybin mushroom provided by site staff and not use any other psilocybin (or similar drug) in any form for at least 30 days prior to Study Day 1 and for 30 days following the single-dose study drug treatment.
9. Is willing to wear, sync daily, and charge twice weekly a provisioned health tracking wearable device every day during sleep and daily activity. If the participant already has the same, or compatible device, they can use their own.
10. Agree to not use any psychoactive drugs, partake alcoholic beverages, self-administer ondansetron (or other selective serotonin reuptake inhibitors 'SSRIs', serotonin-norepinephrine reuptake inhibitors, 'SNRIs' and monoamine oxidase inhibits, 'MAOs'), cannabis, and/or any other non-routine PRN medications within 24 hours of Study Day 1. Exceptions include daily use of caffeine, nicotine, and opioid pain medication
11. Be stable on any pre-study medications and/or psychotherapy regimen prior to study entry. Agree to inform physician(s)/clinician(s) providing current care about your participation in the study (or permit the research site study staff to do so). Agree to report any changes in medication or psychotherapy treatment regimen during the study, to study staff.
12. If female and of childbearing potential, the participant is eligible for the trial only with a negative urine pregnancy test during Screening and on Study Day 1. [If a result is uncertain (e.g., potential false positive), a serum human chorionic gonadotropin (hHCG) test may be performed prior to the administration of the study drug.] Fertile females agree to use a highly effective form of birth control during the 30-day posttreatment period and must confirm that they have no intent to try to become pregnant or any need to breastfeed during this period.
    - Adequate birth control methods include intrauterine device (IUD), injected or implanted hormonal methods, oral hormones plus a barrier contraception, or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e., condom and diaphragm, condom or diaphragm and spermicide, oral hormonal contraceptives and spermicide or condom). Not of childbearing potential is defined as permanent sterilization or postmenopausal females.
13. Be proficient in reading and writing in English and able to effectively communicate with site staff.
14. Agree not to participate in any other interventional clinical trials during the study.

5.1.2 Exclusion Criteria

1. Currently uncontrolled hypertension. (>140/90 at Screening and >145/95 on Study Day 1).
2. History of recent seizure (within 3 months of Study Day 1).
3. History of stroke or transient ischemic attacks.
4. Preexisting history of valvulopathy or pulmonary hypertension.
5. A marked prolongation of QT interval (i.e., QT ≥450 msec) over a series of 3 ECGs performed within 5-6 minutes.

6. Currently uncontrolled diabetes (HbA1c > 8.0%).
7. Potential for adverse drug-drug interactions such as the use of centrally-acting serotonergic agents within 24 hours prior to and for 72 hours following study drug administration on Study Day 1.
8. Significant suicide risk defined by (1) suicidal ideation as endorsed on items 4 or 5 on the Columbia Suicidal Severity Rating Scale (C-SSRS) within the last 6 months, at Screening, or at Baseline (Visit 1), or; (2) suicidal behaviors within the last 12 months as assessed by C-SSRS.
9. Patients with severe anxiety and depression measured as following: Participants with scores of 15 & above on Generalized Anxiety Disorder-7 (GAD-7) scale, and/or with scores of 20 & above on Patient Health Questionnaire-9 (PHQ -9).
10. Are pregnant or nursing or are women of childbearing potential who are not practicing a highly effective means of birth control.
11. Have any allergies or contraindication to psilocybin mushrooms.
12. Current users of psilocybin, LSD, DMT, Ayahuasca, Peyote, mescaline, and ketamine over the past 30 days will not qualify for the study unless the use of these agents is stopped for 30 days prior to Study Day 1 and the participant agrees to not use these (or similar) agents for 30 days after Study Day 1.
13. Are not able to attend face-to-face visits at the study site or plan to move out of the area prior to the 3-month LTFU visit.
14. Have any current problem that, in the opinion of the Investigator or Medical Monitor, might interfere with an individual's participation in the study or confound the assessment of safety and/or efficacy of the study drug.

5.2. Participant Numbering

Prior to enrollment, participants that sign an ICF will be assigned a 3-digit screening number, assigned sequentially, starting at 001 (through 099). Participants who meet the protocol's eligibility criteria and are scheduled for a Study Day 1 visit will be assigned a 5-digit participant number. The first two digits will be "01" and will identify the study site and be linked to the next three-digit number also will be assigned sequentially starting with 101.

- For example, the first three potential participants that are screened would be assigned: 001, 002 and 003. If the second and third participants qualify for the trial and are scheduled for a Study Day 1 visit, they will be assigned 01-101 and 01-102, respectively. If two additional individuals are screened, they would be assigned screening numbers of 004 and 005. If only 005 is found to be eligible and scheduled for Study Day 1, that participant will be assigned 01-103.

5.3. Withdrawal of Participants

Participants can withdraw their consent to continue participating in this trial at any time, without prejudice and with no impact on their subsequent medical care.

The Investigator can withdraw a participant from continued participation in the trial if, in his or her clinical judgment, it is in the best interest of the participant or if the participant cannot

comply with the experimental procedures and related visits that are critical to assess the safety of the investigational product.

Regardless of the reason, any withdrawal (or discussion about withdrawing) from continued participation in the trial will be recorded in the participant's personal medical record (i.e., source document). If a patient prematurely discontinues participation in the trial, the date of and reason(s) for discontinuation will be recorded in the electronic case report form (eCRF).

Among the reasons that may require participants to prematurely discontinue participation is that they may not be able to comply with one or more eligibility criteria such as the prohibited use of certain concomitant medications. If the Investigator withdraws a participant from the trial, the reason(s) for the decision will be explained to the participant. If the Investigator feels it is needed, the participant may be referred for continued PTSD (and/or other medically necessary) care.

As necessary, participants that are withdrawn due to AEs will continue to be clinically monitored until the event resolves, unless the participant refuses to do so.

Whenever possible, the Investigator or another member of the research study team will ask any participant that chooses to withdraw or is withdrawn by the Investigator to return to the study site as soon as convenient to undergo the protocol's mandated tests, examinations, procedures and assessments that are required for the Day 30, EoT visit. Nonetheless, the decision to return to the study site and undergo some or all of the activities required at the EoT visit rests entirely with the participant. As noted in Section 5.2, the patient should not be coerced into continuing to be involved in the trial, even in a less demanding manner.

6.STUDY DRUGS

6.1. Product Description

The product is a whole dried organic hallucinogenic mushroom (RTT1121 also called JMF-01), which has been milled and then subsequently formulated into a solid chocolate dosage form (drug product) prior to administration to patients. The total dose is standardized to 30 mg (± 10%) of psilocybin, delivered as three individual units of chocolate. Each chocolate corresponds to 10 mg of psilocybin.

- The whole organic psilocybin mushrooms are obtained from a Drug Enforcement Administration (DEA)-approved supplier. The composition of the mushrooms is verified by a qualified laboratory.

6.2. Packaging and Labeling

Organic whole dried ground psilocybin mushrooms will be placed in a plastic container labelled with the investigational product dosage of 10 mg of psilocybin, (psilocybin is approximately 1% of the total mushroom weight), batch number, participant number, and date of use. DEA Schedule C-I Drug labels will indicate the manufacturer, expiration date, study identification, and that study drug is only to be administered in the presence of study investigators.

6.3. Product Storage and Handling

Psilocybin-containing mushrooms are a Schedule 1 controlled substance and will be stored and

handled in compliance with relevant institutional policies, federal and state regulations, and in accordance with DEA requirements.

Psilocybin mushrooms may be stored at room temperature (68-77 °F).

6.4. Product Stability

Information on the concentrations of psilocybin and other active metabolites and the stability of these compounds will be provided by a certified testing laboratory.

6.5. Dose and Administration

6.5.1 Dose

For the visit, study participants will self-administer a total dose of 30 mg (± 10 %) of psilocybin, derived from whole, dried, ground organic psilocybin mushrooms (RTT1121 also called JMF-01), which has been milled and formulated into 3 solid units of chocolate. Each chocolate contains to 10 mg of psilocybin and all three units of chocolate will be consumed concurrently during a single dosing session.

6.5.2 Route of Administration & Fasting State Prior to Dosing

Whole, dried, ground, organic psilocybin mushrooms are intended to be taken orally as a chocolate preparation. Participants will self-administer the psilocybin mushrooms on Study Day, 1 in a fasting state, following completion of the protocol's required pre-dose tests, examinations and assessments.

6.6. Product Supply and Accountability

The Investigator (or qualified designee), under the direction of a Schedule I license holder, will supply participants with whole organic psilocybin mushrooms for self-administration. All psilocybin mushrooms dispensed during the study will be tracked by date dispensed, dose, batch, and participant number.

Drug Dispensation and Disposition Forms will be provided to the study site to track drug supply and accountability throughout the study. Records pertaining to the use of Schedule I compounds will be maintained in accordance with relevant federal and state Regulations, and institutional policies, where applicable.

6.7. Allowed and Prohibited Medications and Therapies

6.7.1 Prohibited Medications/Treatments

The consumption of synthetic psilocybin or psilocybin mushrooms (other than the single dose of the whole organic mushroom study drug) as well as LSD, DMT, ayahuasca, peyote, mescaline, and ketamine are forbidden during the study (and for at least 30 days prior to Study Day 1).

Medications with the potential for adverse drug-drug interactions including centrally acting serotonergic agents also are forbidden during the study.

Participants must agree not to participate in any other interventional clinical trials and/or additional treatments during this study.

6.7.2 Permitted Psychotherapy

Participants will undergo regular psychotherapy.

7. STUDY PROCEDURES AND EVALUATIONS

7.1. Timing of Procedures

Procedures will be conducted according to the Schedule of Events Table 1.

7.1.1 Recruitment of Participants

Participants will be recruited via IRB-approved materials which may include letters of referral sent to psychiatrists and psychotherapists, primary care providers, advertisements or announcements placed in appropriate locations or on appropriate internet sites and websites. Participants also may be made aware of the trial by word of mouth.

Approximately 30 potential participants with PTSD may need to be screened to identify 24 participants that will receive the single dose of study drug. This figure assumes a screen failure rate of approximately 30%. In addition, participants that are treated, but that prematurely discontinue participation in the trial on or before Study Day 3, for any reason except if due to an adverse event, may be replaced at the discretion of the Investigator.

7.1.2 Pre-screening

Prospective participants may be interviewed by telephone to determine whether they might be suitable candidates to participate in the trial. At the start of the telephone interview, interviewees will provide verbal consent confirming that they are willing to share personally identifiable information and their personal health information to determine if they are likely to qualify for participation in the trial.

The pre-screening interview will include questions about the participant's medical and psychiatric history, current treatment, etc. The interviewees will be asked to provide responses to the 17-question Life Events Checklist for DSM-5 (LEC-5) and the 20-question PTSD Checklist for DSM-5 (PCL-5). Qualified study site staff will provide individuals that pass the pre-screening assessment with IRB-approved study information and consent materials for review and consideration.

- If the prospective participant is not eligible or not interested in taking part in the trial their personal information will be destroyed at, apart from the summary reason for ineligibility, which will be retained on the Screening Log. An eCRF will not be completed for candidates who are not enrolled.

Pre-screening information will be retained for candidates who provide specific permission via verbal consent for utilization and retention of this information and who and provide written informed consent to participate in the trial. The Screening Log will be completed to include the qualified participant's screening number. The Screening Log will be maintained and kept up-to-date and be available for review by the study site monitor.

Table 1

Schedule of Events

Activity	Pre-Screen	Screening Period		Day 1	Day 2	Day 4 (Virtual)	Day 8	EoT Day 30	LTFU
		-30 - to -1 (Can be extended)			24 hours	72 hours	1 week (±1 day)	1 Month (±5 days)	3 Month (±7 days)
		Prior to Study Day 1							
Pre-Screen Verbal Consent[1]	X								
LEC-5^		X							
PCL-5^		X							
Informed Consent		X							
Medical History	X	X		X					
Concomitant Medications	X	X		X	X	X	X	X	X
Eligibility Criteria	X	X		X					
Height / Weight[2]		X					X	◆[14]	
Physical Exam[3]		X					X	◆[14]	
Vital Signs[4]		X		X	X		X	X	X
Urine Pregnancy Test[5]		X							
Urine Drug / Alcohol Tests		X		X				X	X
Clinical Laboratory Tests[6]		X[6]		X			X	X	
Electrocardiogram[7]		X		X			X		
Dispense/Collect Wearable		X						◆[14]	X
Saliva – Epigenetic Test				X			X	◆[14]	
Pharmacokinetic Test[8]				X					
Administer Study Drug				X					
One-to-One			X[15]						
Group Session				X[15]	X	X			
Ceremony				X					
GAD-7[9]		X		X	X	X	X	X	X
PHQ-9[10]		X		X	X	X	X	X	X
NIH-HEALS		X		X	X		X	X	X
BPI		X		X	X	X	X	X	X
C-SSRS[11]		X		X	X	X	X	X	X
POMS[12]				X					
SDS		X						X	
WCS				X			X	X	
MEQ30-revised				X				X	
CEQ				X				X	
5D-ASC				X					
AUDIT[13]		X						◆	X
DUDIT[13]		X						◆	X
Adverse Events					X	X	X	X	X

Footnotes:

1. Pre-Screen: Study site staff should obtain verbal consent to collect information to assess potential eligibility for the trial. If the individual does not qualify or chooses not to participate, the information collected will be deleted, save for more general, non-identifiable, information recorded on the Screening Log.
2. Height / Weight: Height and weight should be measured at Screening, but only weight will be measured at the Study Day 8 and EoT visits, respectively.
3. Physical Examination: The physical exam should be targeted to head, eyes, ears, nose, throat (HEENT), abdomen and extremities. A brief neurological exam also should be performed on cranial nerves 2 through 12 as well as assessments of motor reflexes and cerebellar function.
4. Vital Signs: Measure body temperature, pulse oximetry (SpO_2), heart rate, respiratory rate, and blood pressure
5. Urine Pregnancy: A urine sample should be collected for all females of childbearing potential. If needed, a serum-HCG test can be done to confirm an initial positive result.
6. Clinical Laboratory Tests: Blood samples will be collected to perform clinical laboratory evaluations. A urine sample, for urinalysis, only will be collected at Screening.
7. Electrocardiogram: A 12-lead ECG should be obtained. If there is a finding of QT interval prolongation (i.e., > 450 msec), then triplicate ECG recordings should be done within 5 (to 6) minutes for confirmation. If confirmed, the participant is not eligible to participate in the trial.
8. Pharmacokinetic: Blood samples for PK testing should be obtained at the following timepoints on Study Day 1: up to 30 minutes prior to study drug administration and then at the following timepoints after dosing — 30 minutes (±2 mins), 60 minutes (±5 mins), 90 minutes (±5 mins), 120 minutes / 2 hours (±5 mins), 4 hours (±15 mins) and 8 hours (±15 mins)

^ To qualify for treatment, participants must self-report at least one traumatic event via the LEC-5 that the clinician considers causative for a diagnosis of PTSD; in addition, they must score at least 33 on the PCL-5

9. GAD-7: If a participant's score is ≥15 at Screening or on Study Day 1 (prior to study drug administration), the participant is not eligible for treatment.
10. PHQ-9: If a participant's score is ≥20 at Screening or on Study Day 1 (prior to study drug administration), the participant is not eligible for treatment.
11. C-SSRS: If at Screening or on Study Day 1 a participant's 'suicidal' assessment is scored as Category 4 (i.e., Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or Category 5 (Active Suicidal Ideation with Specific Plan and Intent), the participant is not eligible to continue to participate in the trial and should be referred for appropriate psychiatric care.
12. POMS: On Study Day 1, after all protocol-mandated activities are complete, the clinician will assess the result of the POMS. If the posttreatment POMS score is not ≤125% of the baseline, pre-dose, value, the patient should be held overnight for observation. [Otherwise, if the score is ≤125% of the baseline, and if there are no other problems, the patient may be discharged to home (accompanied by a trusted adult).
13. AUDIT / DUDIT: The AUDIT and DUDIT should be completed at the Study Day 30 / End-of-Treatment visit if a participant prematurely discontinues from the trial (for any reason) and will not undergo the 3-month, Long-Term Follow-up visit.
14. ◆: The diamond reflects tests, examinations, assessments or other procedures that are to be completed the EoT visit if a participant is prematurely discontinued from further involvement in the trial and the particular protocol-mandated activity was not performed at the Study Day 8 visit.
15. **The One-to-One session as well as the Group session require participants to return to the study site on separate days. [Thus, the Screening Period can require three (3) visits to the study site.]**

Table 2

Study Day 1 Schedule of Events

Activity	Pre-Dose	Dose	Post Dose								
		Time 0	30 mins	60 mins	90 mins	120 mins	150 mins	180 mins	240 mins 4 hours	4.5, 5.0, 5.5, 6.0, 6.5, 7.0 and 7.5 hours	480 mins 8 hours
Medical History	X										
Concomitant Medications	X										
Eligibility Criteria	X										
Height / Weight[2]	X										
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X*	X
Urine Pregnancy Test[5]	X										
Urine Drug / Alcohol Tests	X										
Clinical Laboratory Tests[6]	X										
Electrocardiogram[7]	X										
Saliva – Epigenetic Test	X										
Pharmacokinetic Test[8]	X	X	X	X	X	X	X	X	X		X
Administer Study Drug		X									
Ceremony	X										
GAD-7[9]	X										X
PHQ-9[10]	X										X
NIH-HEALS	X										
BPI											X
C-SSRS[11]	X										X
POMS[12]	X										X
WCS											X
MEQ30-revised											X
CEQ											X
5D-ASC											X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

*Vital signs measured every 30 minutes, (i.e., 2 times per hour) during hours 4, 5, 6 and 7.

7.1.3 Screening Period (Day -30 to -1)

If after the pre-screening telephone interview, the study site staff and/or the investigator feel the candidate may be suitable for the study, a Screening visit will be scheduled.

The initial Screening Visit will include the following protocol mandated activities, tests, examinations, assessments and procedures:

- Explain and obtain written informed consent from the candidate prior to performing any study-specific tests or evaluations.
- Issue a 3-digit screening number and record the appropriate information on the Screening Log.
- Review the participant's medical and psychological history including current and past medications and therapies.
  - Have the participant sign a medical release form to allow the Investigator to review his/her medical records to ensure the participant has no underlying medical conditions that would preclude their participation in the trial and confirm the PTSD diagnosis.
- Review the LEC and PCL-5 checklists.
- Review with female participants of childbearing potential their ability to become pregnant and commitment to practice appropriate birth control as defined in this protocol for the total duration of the study.
- The following clinician rating scales and participant QoL and PRO instruments should be administered and/or completed by the participant, respectively:
  - LEC-5 (at least one traumatic event causative for a diagnosis of PTSD)
  - PCL-5 (a score of at least 33)
  - GAD-7 (scores of ≥15 will exclude the participant)
  - PHQ-9 (scores of ≥20 will exclude the participant)
  - NIH HEALS
  - BPI
  - C-SSRS (category ratings of 4 or 5 will exclude the participant)
  - SDS
  - AUDIT
  - DUDIT
- Collect vital signs (blood pressure, pulse, body temperature, respiratory rate and pulse oximetry).
  - Perform a medical history directed physical examination. The examination will involve the following procedures:
  - Height/weight.
  - Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities.

  - Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function).
  - Obtain 12 lead ECG
- Collect urine for the following laboratory analyses:
  - Urine pregnancy test in women of childbearing potential.
  - Qualitative rapid urine drug screen.
  - Qualitative urine ethyl glucuronide (EtG) test to assess alcohol consumption.
- Collect a blood sample for clinical laboratory evaluations.
- If, upon examination, there are questions raised about possible medical problems, the investigator can request an additional review of the participant's medical records and order additional tests or assessments, as indicated.
- Assess eligibility criteria. If the participant meets all initial screening criteria, site staff will schedule the treatment visit for Study Day 1.
- Obtain participant's ring size and dispense the health tracking wearable device and provide instruction on its use (including daily wear, recharging, etc.). If a participant has the same (or compatible) device, they can use their own.
- Each participant will take part in an introductory psilocybin preparatory session with trained staff after confirming eligibility at the initial Screening visit and prior to Study Day 1. During these sessions, participants will engage in discussions with trained facilitators about any goals or desires they have, spiritual beliefs, or world views, and any beliefs about death or the afterlife. Participants also will be asked about their intentions with the psilocybin session.

  The trained staff will inform participants of what to expect during their psilocybin-assisted session. Participants will be provided with (i) information about psilocybin mushrooms, (ii) expected psychoactive and physical effects, and (iii) methods for documenting and managing side effects of psilocybin mushrooms, if/when they occur.

  Information also will be shared about community support, breathing strategies, as well as rescue psychotherapy or medications available to use if needed.
  - Each participant will also participate in a group education session conducted by the lead therapist regarding the treatment and ceremony following the individual preparation session.
- Participants will be instructed to bring their pain medication with them on Study Day 1 and will be educated on how their pain will be managed, including having the study site provide additional pain medication should their pain increase after the 3 doses of whole organic psilocybin chocolate are self-administered.
  - Participants who use opioid analgesics will be instructed to maintain their usual regimen.
    - Input will be obtained from the participant's regular clinical providers on appropriate pain management for the participant during the trial, particularly in the case of

analgesics associated with adverse reactions of concern with psilocybin (e.g., QTc prolongation with methadone).

- Participants will identify a trusted adult who will accompany them on their ride home and the same or another adult who will stay with them overnight at their residence after being discharged from the study site on Study Day 1.

7.1.4 Study Day 1

Study Day 1 will be scheduled after the participant completes all the required Screening Period activities and is deemed to remain eligible for treatment with the study drug. There are three portions of the Study Day 1 visit including: consist of (i) confirming eligibility and performing baseline measurements for multiple primary, secondary and exploratory endpoint assessments, prior to study drug administration, (iii) self-administration of study drug under supervision, and (iv) observing participants for 8-hours post-dose for adverse events including collection of blood samples for pharmacokinetic profiling, completing clinician rating scales, among other activities.

The following protocol mandated activities, tests, examinations, assessments and procedures will be performed on Study Day 1:

Pre-Dose and Baseline Assessments

- Inquire about any changes in the participant's health and review concomitant medications/therapies (including psychotherapy and healthcare utilization).
- Obtain vital sign measurements.
- Perform a 12-lead ECG.
- Obtain blood samples for:
  - Clinical laboratory evaluations.
  - PK profiling –30 minutes (±2 mins).
- Obtain urine samples for:
  - Pregnancy test in women of childbearing potential.
  - Qualitative rapid urine drug screen.
  - Qualitative urine ethyl glucuronide (EtG) test to assess alcohol consumption.
- Obtain saliva sample for epigenetic analysis.
- Review all eligibility criteria.
- Issue a research participant identification card ("wallet card") that indicates they are a research participant and may test positive for drugs. The card includes the Investigator's contact information, the telephone number for a 24-hour hotline for participant support, and instructions on how/when to present the card.
- The following clinician rating scales and participant QoL and PRO instruments should be

administered and/or completed by the participant, respectively:

- POMS
- BPI
- C-SSRS (category ratings of 4 or 5 will exclude the participant)
- GAD-7 (scores of ≥15 will exclude the participant)
- PHQ-9 (scores of ≥20 will exclude the participant)

- Obtain/confirm the name and telephone number of an emergency contact from the participant for use throughout the study.

Study Medication Administration

Provided the participant remains eligible, they will undergo a symbolic ceremony in which intentions are set and then be instructed to self-administer the study drug.

- The participant will self-administer, under observation, a whole, dried, ground organic psilocybin mushroom (RTT1121 also called JMF-01) which has been milled and formulated into 3 solid chocolates.
  - A physician will be onsite, or if observing via video conferencing can reach the study site within 10 minutes in case of a medical emergency.

Post-Dose Monitoring and Assessments

Following the self-administration of the single dose of study drug, participants will be instructed to lie down wearing eyeshades and listen to a preselected music playlist via headphones and speakers. Participants will be closely monitored for medical and psychological (including psychosis) adverse effects to ensure their safety and well-being. Participants also will be assessed via clinician rating scales.

In addition to the therapists (and group) support provided, a trained therapy dog also will be available in the dosing room to offer additional support, if requested by the participant.

- Vital signs are to be measured every 30 minutes for at least 8 hours following study drug administration.
  - If vital signs are abnormal at 8 hours, the participant will remain at the study site for continued observation until the measurements return to baseline values, or the Investigator deems that not further monitoring is needed. Vital sign measurements listed below may be considered abnormal; (however, the Investigator may override these values):
    - Blood pressure above 140/90 mmHg
    - Heart rate outside the range of 50-90 beats per minute
    - Respiratory rate
    - Pulse oximetry – SpO2 ratio <92%
- Blood samples for PK profiling will be collected at the following timepoints
  - 30 minutes (±2 mins)

60 minutes (±5 mins)
- 90 minutes (±5 mins)
- 120 minutes / 2 hours (±5 mins)
- 4 hours (± 15 minutes)
- 8 hours (±15 minutes)

- Manage participant's complaints of pain and administer pain medication as warranted and record the type(s) and amount(s) administered.
- Nearing the 8-hour timepoint, the following clinician rating scales and participant QoL and PRO instruments should be administered and/or completed by the participant, respectively:
  - GAD-7
  - PHQ-9
  - C-SSRS
  - MEQ30-revised
  - CEQ
  - 5D-ACS
  - WCS
  - BPI
  - POMS (post-treatment score must be ≤125% of baseline, pre-dose, value otherwise patient should be held overnight for observation)

After all assessments are completed, the effects of the study drug have dissipated and the participant is fully ambulatory, displays good balance and is psychologically stable, he/she may be discharged to home so long as they are accompanied by a trusted adult. The study site is to be notified when the participant has returned home safely, and in the absence of receiving a confirmatory phone call, study site staff will contact the participant. In addition, the participant will confirm if the same, or another, adult will stay with them overnight at their residence.

However, if the participant requires continued monitoring for one or more ongoing adverse events (including abnormal vital signs), or if the participant's assessed levels of anxiety, depression and/or suicidal ideation are found to be above pre-dose (baseline) levels, the participant should be evaluated by the Investigator (or another physician) and remain at the study site overnight for observation.

During overnight observation, the participant will be monitored by a nurse and reevaluated by the Investigator (or other physician) in the morning. The outcome of the evaluation will determine if the participant continues to participate in the trial and complete protocol-mandated, Study Day, activities. Regardless, the participant will be discharged to home on Study Day 2 only after the anxiety, depression and/or suicide ideation symptoms are at or below the respective baseline levels.

If symptoms persist, the Investigator will arrange for needed medical care including having the participant transferred to an emergency department at a nearby hospital and/or inpatient psychiatric

center.

7.1.5 Study Day 2

On Study Day 2, the participant will return to the study site, as reasonably close to 24 hours after the time of study drug administration. The following protocol-mandated procedures, assessments and activities will be performed:

- Review concomitant medications
- Query the participant in a non-suggestive manner to identify any adverse events
- Obtain vital signs measurements
- Have participant join a group integration session
- Administer and/or have the participant complete the following clinical rating scales and participant QoL and PRO instruments, respectively:
  - GAD-7
  - PHQ-9
  - BPI
  - C-SSRS

7.1.6 Virtual Phone Session, Study Day 4

On Study Day 4, approximately 72 hours after study drug administration, the participant will have a 1:1 support integrative therapy session. The intent of the session is to allow the participant and trained facilitators to discuss the feelings, thoughts, and experiences that occurred during the psilocybin session, and consider whether the participant attained his or her initial intentions and will discuss ways in which the participant has/can integrate(d) this into their everyday life. The facilitator(s) will also review mindfulness techniques.

During the Study Day 4 virtual phone visit the following protocol-mandated activities will be completed:

- Review concomitant medications
- Query the participant in a non-suggestive manner to identify any adverse events. If the participant reports any concerning (or serious) AEs, the study site staff member will direct the participant to receive appropriate medical (or mental health) care.
- Administer the following clinical rating scales and participant QoL and PRO instruments, respectively:
  - GAD-7
  - PHQ-9
  - BPI
  - C-SSRS

7.1.7 Study Day 8

One week following Study Day 1, participants will return for the Study Day 8 visit wherein the following protocol-mandated tests, examination, procedure and assessments will be performed.

- Inquire about any changes in the participant's health in a non-suggestive manner and review concomitant medications/therapies (including psychotherapy and healthcare utilization).
- Perform a brief physical exam and obtain weight.
- Obtain vital sign measurements
- Perform a 12-lead ECG
- Obtain blood samples for clinical laboratory evaluations
- Obtain saliva sample for epigenetic analysis
- Review participant use of health tracking wearable device; provide instruction on compliance as needed.
- Administer and/or have the participant complete the following clinician rating scales and participant QoL and PRO instruments, respectively:
  - GAD-7
  - PHQ-9
  - NIH HEALS
  - BPI
  - C-SSRS
  - WCS

7.1.8 Study Day 30 / End-of-Treatment (EoT) Assessments

One month after Study Day 1, participants will return to the study center on Study Day 30.

Likewise, any participant that self-administered study drug on Study Day 1, but that prematurely discontinues participation in the trial, for any reason, should be encouraged to undergo an End-of-Treatment visit. If the participant was discontinued prior to the Study Day 8 visit, additional tests and examinations will be performed at the EoT visit. For discontinued participants, the Study Day 8 visit should be scheduled as soon as practical to ensure collection of needed safety, and preliminary efficacy data.

- As noted in Section 8.1.1, participants that are prematurely discontinued before Study Day 3, for any reason except due to an adverse event, may be replaced, at the discretion of the Investigator.

The protocol-mandated tests, examinations, assessments and procedures to be performed during the Study Day 30 / EoT visit are presented below:

- Inquire about any changes in the participant's health in a non-suggestive manner and review concomitant medications/therapies (including psychotherapy and healthcare utilization).

- Perform a brief physical exam and obtain weight (only if Study Day 8 visit was not completed).
- Obtain vital sign measurements.
- Obtain blood samples for clinical laboratory evaluations.
- Obtain saliva sample for epigenetic analysis (only if Study Day 8 visit was not completed).
- Obtain urine samples for:
  - Qualitative rapid urine drug screen.
  - Qualitative urine ethyl glucuronide (EtG) test to assess alcohol consumption.
- Review participant's use of health tracking wearable device and collect the device and download the data to the trial database (if the participant prematurely discontinued participation in the trial and will not be undergoing the 3-month Long Term Follow-up visit).
- Administer and/or have the participant complete the following clinician rating scales and participant QoL and PRO instruments, respectively:
  - GAD-7
  - PHQ-9
  - BPI
  - NIH HEALS
  - C-SSRS
  - SDS
  - AUDIT (only if the participant was prematurely discontinued)
  - DUDIT (only if the participant was prematurely discontinued)

If the participant prematurely discontinues from the trial, this will be their last study visit, unless there is an ongoing adverse event that will continue to be monitored until resolution or until the Investigator and Medical Monitor determine that no additional follow-up is medically necessary.

Otherwise, the participant will return to the study site for the final 3-month, LTFU, visit.

7.1.9 3-Month Long-Term Follow-up (LTFU) Visit

Approximately three months (i.e., 90 days) after Study Day 1, participants will return for the final, 3-month, Long-Term Follow-up (LTFU) visit. At this visit, a number of protocol-mandated tests, examinations, assessments and procedures will be done as described below.

- Inquire about any changes in the participant's health in a non-suggestive manner; however, any changes noted will not be considered adverse events unless they either were noted prior to the Study Day 30 / EoT visit and/or are considered to be 'possibly' or 'probably' related to study drug administration.
- Review concomitant medications/therapies (including psychotherapy and healthcare utilization).
- Perform a brief physical exam and obtain weight (only if Study Day 8 visit was not completed).

- Obtain vital sign measurements.
- Obtain urine samples for:
  - Qualitative rapid urine drug screen.
  - Qualitative urine ethyl glucuronide (EtG) test to assess alcohol consumption.
- Review participant's use of health tracking wearable device and collect the device and download the data to the trial database.
- Administer and/or have the participant complete the following clinician rating scales and participant QoL and PRO instruments, respectively:
  - GAD-7
  - PHQ-9
  - BPI
  - NIH HEALS
  - C-SSRS
  - AUDIT
  - DUDIT

Upon completion of the 3-month, long-term follow-up visit and after the study site staff obtain all outstanding data, participants will have completed the study, except if there is an ongoing adverse event that the Investigator and/or Medical Monitor believe warrants continued monitoring until resolution or until it is determined that no additional follow-up is medically necessary.

7.2. Pharmacokinetic Assessments

The pharmacokinetics (PK) of psilocin (the major active metabolite of psilocybin) will be investigated following self-administration of a single dose of a whole organic psilocybin mushroom.

The PK profile of psilocin will be assessed in plasma on Study Day 1. Blood samples will be processed and analyzed for concentrations of psilocin by a validated method. On Study Day1, participants must self-administer the psilocybin mushroom in a fasted state and will remain fasted for a minimum of 4 hours following the administration of study drug.

The specific collection times for PK blood samples are outlined below.

Predose:

- Up to -30 minutes before study drug administration

Post Dose:

- 30 minutes / 0.5 hours (± 2 mins) post dose
- 60 minutes / 1.0 hour (± 5 mins) post dose
- 90 minutes /1.5 hours (± 5 mins) post dose
- 120 minutes / 2 hours (±5 mins) post dose
- 4 hours (±15 mins) post dose

- 8 hours (±15 mins) post dose

7.3. Premature Termination of the Trial

The Investigator has the right to terminate this trial at any time. If the trial is terminated, the Investigator is to promptly inform the study participants and the Institutional Review Board (IRB) and will arrange appropriate follow-up. If the trial or study is discontinued, all procedures and requirements pertaining to the archiving of documents will be observed. Study materials will be treated in accordance with federal and local regulations.

8.SAFETY ASSESSMENTS

8.1. Adverse Events

AEs and SAEs will be noted at each study visit. Participants will be queried to determine if anything has changed in their health status since the last visit (following Study Day 1), using non-leading questions. [For AE collection and reporting requirements, see Section 10 of the protocol.]

8.2. Vital Signs

Participant vital signs, including blood pressure (systolic/diastolic), heart rate, respiratory rate, pulse oximetry and body temperature, will be assessed at each study visit.

Vital signs should be measured after the participant has been sitting in a relaxed manner for at least 5 minutes. Blood pressure measurements will be obtained with the participant in a sitting position.

8.3. Clinical Laboratory Assessments

Pregnancy Test: A urine pregnancy test for female participants of childbearing potential will be performed at Screening and on Study Day 1, prior to administration of the study drug.

Drug and Alcohol Tests: A qualitative rapid urine drug and an EtG urine test will be performed to test for recent alcohol consumption at Screening, on Study Day 1, prior to administration of the study drug and at the EoT visit.

- *Clinical Laboratory Testing*: Blood and urine sampling for clinical laboratory assessments will be performed at the study site or closest available facility. However, a urine sample, for urinalysis, only will be collected at the Screening visit.
  - Results from the blood and urine tests will determine eligibility during the Screening Period.

  Urinalysis results will include color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, urobilinogen. If clinically warranted, reflex testing to assess aberrant results (e.g., for a positive leukocyte esterase result) may be done at the discretion of the investigator.

  Blood analyses will include a complete blood count for hematology parameters along with serum electrolytes, a metabolic profile and liver enzyme and renal function tests for blood chemistry parameters.

Table 3- Hematology Parameters

White blood cell count (WBC)	Red blood cell count (RBC)
WBC Differential count	Mean corpuscular volume (MCV)
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)

Table 4- Chemistry Parameters

Glucose	Alkaline phosphatase (ALP)
Total bilirubin	Lactose dehydrogenase (LDH)
Blood urea nitrogen (BUN)	Aspartate aminotransferase (AST/SGOT)
Creatinine	Alanine aminotransferase (ALT/SGPT
Sodium	Gamma-glutamyl transpeptidase (GGT)
Potassium	Prothrombin time
Serum calcium	Albumin
Magnesium	Total protein
Phosphate	Bilirubin
Carbon dioxide	

- The Investigator will use normal ranges provided by the central laboratory.

Epigenetic Analysis: DNA methylation will be measured in the lab of Dr. Candace Lewis at Arizona State University.

DNA will be extracted from saliva samples with a standard isolation kit (Qiagen, Hilden,Germany). Sample yield and purity will be assessed using fluorometric methods (Quant-iT™ PicoGreen™ dsDNA Assay Kits; Invitrogen).

Approximately 500 ng of DNA will undergo bisulfite treatment using the EZ-96 DNAm Kit (Zymo Research, Irvine, CA). DNAm will be quantified using the Infinium MethylationEPIC v2 BeadChip run on an Illumina iScanSystem (Illumina, San Diego, CA).

Raw IDAT files will be preprocessed in "R" with the minfi package[55]. Data will be subjected to quality control analyses, which includes quantile normalization, checking for sex mismatches, and excluding low-intensity samples ($p < 0.01$). Data will be normalized and annotated with Illumina CpG site probe names. Using the R package EpiDISH (Epigenetic Dissection of Intra-Sample Heterogeneity, 3.8) RPC method, a proportion of estimated epithelial cells will be generated as a covariate in the statistical models.

8.4. Concomitant Medications and Therapies

Participants will take note of their concomitant use of alcohol, medications, and other drugs, psychotherapy, and health care use and provide this information to the study site staff at their scheduled study visits.

Information about all concomitant prescription, non-prescription (including recreational) and/or over-the-counter drugs and medications as well as herbal dietary supplements, other home remedies will be collected from Screening up to the day of the final, 3-month LTFU visit. The

information to be collected will include the drug/supplement, the reason(s) for use, the dates started and ended (or noted as 'ongoing' at the end of a participant's involvement in the trial), the dosage (if available) and the route of administration.

Medications (including those taken to treat AEs) will be recorded in the participant's medical record and on a concomitant medications electronic case report form (eCRF).

Information on participation in psychotherapy or any other medical intervention that occurs during the course of the participant's involvement in the trial will be recorded on a concomitant therapy eCRF.

8.5. Suicidal Ideation

The Columbia Suicide Severity Rating Scale (C-SSRS) is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial (Posner 2007). It consists of a "Baseline" form that assesses lifetime suicidal ideation, intensity, and behavior, and a form for assessing current suicidal ideation and intensity. The C-SSRS consists of a series of questions and can be administered via face-to- face interview or over the telephone. The C-SSRS is a detailed interview, but the full interview is needed only if the initial screening questions about suicidal ideation and behavior are positive. The screening questions should be completed for every participant and as needed if a participant is showing any signs of being suicidal. For management of suicidal thoughts, see Section 10.3 Risk Mitigation.

9.RISK OF PARTICIPATION

9.1. Risks of Screening, Study Procedures, Assessments, and Measures

Measurements of blood pressure, body temperature, and heart rate, respiration rate and pulse oximetry will be taken during the trial to assess study drug effects and monitor participant safety. Participants may experience mild discomfort from having blood pressure assessed. Submitting to a full medical examination also may cause discomfort or psychological distress. Since medical examinations are required to establish eligibility for the study, it cannot be omitted from the protocol.

Participants also may have minor discomfort from phlebotomy procedures to collect blood samples for clinical laboratory evaluations and PK profiling, respectively.

Providing a saliva sample is considered an easy procedure and at worst may cause the participant to temporarily feel a sense of dry mouth.

Psychological assessments will be obtained through interviews or self-assessments. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of symptoms from life-threatening illness are used during screening, they cannot be avoided. The Investigator and trained staff have experience working with people with life-threatening illness, and they will seek to reduce anxiety and distress during these interviews.

The Investigator and study site staff (and the institution) will take all reasonable measures to maintain patient confidentiality and protect all personally identifiable and personal health information. Nonetheless, no guarantee can be made that there will not be a data breach or that information about the participant's involvement in this trial will not be disclosed.

9.2. Risks of Psilocybin

The risks of psilocybin mushrooms have been characterized in small clinical trials, including among individuals with anxiety, depression, and life-threatening illness (Goodwin 2022, Lowe 2021, Ross 2021, Griffiths 2016, Ross 2016). In systematic reviews of clinical trials with psilocybin mushrooms, the most common adverse effects reported were transient anxiety, headache, nausea or purging, psychological discomfort, physical discomfort, and autobiographical hallucination (Anderson 2020, Muttoni 2019). Vomiting was reported in one study (Griffiths 2016). Psilocybin also increased blood pressure and heart rate.

No SAEs have been reported for clinical studies involving psilocybin. These clinical trials typically employed one or two high doses of psilocybin but also included strong psychological support for participants both prior to and after dosing which may have supported integration and improved the safety profile.

9.3. Risk Mitigation

The Investigator will address a number of risks by enrolling participants without contraindicating conditions, including psychotic disorders and major medical conditions affecting the heart or lungs, etc. Participants who pose a major suicide risk also will not be enrolled in the study.

Untoward psychological reactions to psilocybin mushrooms will be dealt with by preparing participants for the subjective effects of the substance, and by self-administering the single dose of the psilocybin mushroom under observation by trained facilitators during the Study Day 1 visit who will be able to help address any anxiety or paranoid feelings the participant may experience.

Participants will be informed of the effects that psilocybin mushrooms might have on driving, and they will be advised to avoid driving for a minimum of 24 hours after study drug administration on Study Day 1. Participants will arrange rides home after Study Day 1 with a trusted adult companion. In addition, the same, or another, adult will stay with the participant overnight at their residence.

Potential reproductive risks will be mitigated by restricting enrollment to women who are not pregnant or lactating, and by requiring women of childbearing potential to undergo pregnancy testing prior to study drug administration during Screening and on Study Day 1 and use a highly effective form of birth control until Study Day 30 / EoT visit during the trial.

All study participants will be issued a 'study participant identification wallet card' that indicates that that they may test positive for drugs of abuse (i.e., psilocybin) because they are participating in this clinical trial. The wallet card will include the telephone number for a 24-hour hotline and contain contact information for the Investigator and the IRB, along with the study National Clinical Trial Registry number. The investigator will remind participants that they may still be cited or face penalties for erratic driving and the card will not mitigate this penalty.

All participants' protected health information will be stored in locked files or on secure computer servers and managed in accordance with patient confidentiality procedures pertaining to electronic systems.

The Investigator will discuss with participants the perceived stigma ascribed to psilocybin mushrooms use and to consider the degree to which friends, family, or other people within the community might respond if they observe or learn about the participant's psilocybin mushrooms use.

9.4. Criteria for Termination or Suspension of the Study

The study will be fully enrolled and completed as planned unless one or more of the following criteria are satisfied that require temporary suspension of the study.

- New information regarding the safety or efficacy of the study drug indicates a significant change in the known risk/benefit profile for the drug, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for suspension of the study:
  - The study will be paused if:
  - One participant experiences any of the following during the treatment phase of the trial starting at the time of study drug administration and through Study Day 30/ EoT, even if the participant prematurely discontinued further involvement in the trial:
    - A CTCAE Grade 3 – 5 toxicity which is possibly or probably related to study treatment,
    - A suicide attempt,
    - A marked prolongation of QT interval (i.e., QT ≥450 msec) over a series of 3 ECGs performed within 5-6 minutes,
    - A serious episode of psychosis as determined by the Investigator that requires immediate medical attention,
    - A severe, non-serious, AE possibly related to study treatment,
    - Two participants experience: One or more serious AE's possibly or probably related to study treatment.

The study might also be terminated by the sponsor for the following reasons:

- Slow patient enrollment,
- Data collected lacking quality,
- Poor adherence to protocol,
- Other findings that could lead to the study not meeting its objectives.

9.4.1 Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be constituted that will monitor the study and regularly review the clinical trial safety data. The full scope of responsibilities of the DSMB are outlined in the study protocol (see Section 11.1) and will be included in a DSMB Charter.

The DSMB will have access to the totality of the data to determine if the trial should continue as is, or if changes are warranted to protect the safety and wellbeing of the participants and/or if the trial should be terminated.

9.5. Medical Emergencies

If a participant experiences a medical emergency during the Study Day 1 visit, the Lead Therapist/Investigator (a licensed physician) will manage the participant during the emergency.

In the event a psychological crisis arises during the study, participants will be instructed to call the Participant Hotline as soon as possible. This call will be routed to the Investigator if it is confirmed that there is indeed a crisis. The Investigator (or a qualified designee) will be on call at all times to receive information from the Participant Hotline.

Upon learning about the psychological crisis, the Investigator will assess the AE by:

- Obtaining a detailed history of the event over the phone
- Collecting information on any concomitant medications
- Assessing expectedness, seriousness, severity, and relationship to the study drug
  - All AEs will be assessed regardless of whether they occurred prior to or after self-administration; however, only those events that occur after study drug administration can be attributed to the investigational product.

If the participant requires immediate care, s/he will be referred to the emergency department of the closest hospital. The emergency department and/or hospital staff, the participant's primary care provider, and/or the Investigator may prescribe medications or take steps to stabilize the participant and to help ameliorate and/or resolve the AE.

10. ADVERSE EVENTS

An AE is defined as any untoward or unfavorable medical occurrence in a clinical research study that is observed, measured or reported by a participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected AE is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored by the Investigator or site staff until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and/or Medical Monitor as to whether continued

follow-up of the AE is warranted.

All adverse events will be recorded in the participant's medical record and in the AE form of the eCRF.

The severity of events will be determined by the Investigator as:

- Mild: no limitation in normal daily activity
- Moderate: some limitation in normal daily activity
- Severe: unable to perform normal daily activity

The relationship of the study drug to an AE will be determined by the Investigator, based on the following definitions:

- Not Related
  The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, ie, there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the participant's pre-existing condition.
- Possibly Related
  The administration of the investigational product and the AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product.
- Probably Related
  Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

10.1. Spontaneously Reported Reactions

Commonly expected AEs, that have been compiled from the literature on psilocybin mushrooms reported in studies of human volunteers, are referred to as "spontaneously reported reactions" include transient anxiety, transient headache, transient nausea, and transient paranoia (Dinis-Oliviera 2017).

AEs that are included in the spontaneously reported reactions list will be separated in data analysis for review of expected versus unexpected AEs.

10.2. Serious Adverse Events

The Investigator (or qualified designee) is responsible for determining if an AE is a serious adverse event (SAE) or a non-serious event. An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the participant was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically

might have caused death if it were more severe

- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life- threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the patient/participant or may require intervention to prevent one of the other outcomes listed above

AEs which do not fall into these categories are defined as non-serious. It should be noted that a 'severe' AE need not be serious in nature and that a SAE need not, by definition, be severe.

In addition, any pre-existing event or condition that results in hospitalization should be recorded in the medical history and in the eCRF. The hospitalization would not result in the event or condition being reported as a study-related SAE unless, in the view of the Investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition.

Hospitalization for cosmetic procedures, non-emergency prophylaxis, or abortion does not result in an SAE report unless, in the view of the Investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

10.3. Adverse Event Collection

All AE and SAEs will be collected during the entirety of the participant's involvement in the trial. If a new AE/SAE is reported >30 days after Study Day 1 an up and until the 3-month, LTFU visit, it will be recorded in the participant's medical record and the eCRF; however, unless the event is deemed to be possibly or probably related to the study drug, it will not be recorded as an adverse event.:

- Events related to planned treatments or physician visits for baseline conditions collected in the medical history will not be collected unless there is an exacerbation of the condition.
- Any AE leading to withdrawal from continued participation in the trial protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

10.4. Serious Adverse Event Reporting

All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, must be reported to the Investigator within 24 hours (or at the latest on the following working day) of the any member of the study site staff learning that an event occurred, irrespective of causality.

Contact information for the Medical Monitor and Study Monitor are provided in a separate

document.

- SAEs will be assessed by the Investigator and Medical Monitor for relatedness, seriousness, and unexpectedness, and reported to regulatory agencies, IRBs, and the Investigator according to applicable regulations and policies. The Investigator should notify their respective IRBs according to IRB-specific timelines promptly after assessment.
- SAE reporting to competent authorities (e.g. FDA) is to be done by an authorized delegate.

The Investigator is responsible for the overall safety of the participants, the ongoing safety evaluation of the investigational product for providing the required medical expertise in conjunction with site medical personnel to address trial-related medical questions or problems.

The Investigator (and the Medical Monitor) alone (or jointly) will determine if the SAE will require expedited reporting and what follow-up information is needed for evaluation. If no consensus can be reached, the different assessments and the reasons for this must be summarized in writing. In any case, the most conservative assessment will drive the reporting procedure. The time frame for reporting SAEs to regulatory authorities begins when the Investigator has "initial information" of the event regardless of the form that initial notification takes. Expedited timelines will be followed according to regulatory, institutional, and IRB requirements.

The Investigator is responsible for ongoing safety evaluation of the investigational product and for the prompt notification to regulatory authorities of findings that could adversely affect the safety of participants, impact the conduct of the trial, or alter the IRB's approval/favorable opinion to continue the trial.

Any employee, contractor, or contract organization working on behalf of the Investigator who discovers a serious adverse experience in the context of a clinical trial is responsible for alerting the study site staff trial staff. The Investigator is responsible for collecting serious adverse experience information and submitting safety reports to regulatory agencies.

11. STUDY MONITORING, AUDITING, AND DOCUMENTATION

During or after the clinical trial ends, regulatory authorities, the IRB, and/or representatives of the Investigator may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

11.1. Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) for this clinical trial will be comprised of an independent group of experts that will be established to ensure the safety of participants and the integrity of the data. The DSMB will regularly review study data to monitor participant safety, study conduct, and progress, and will make recommendations regarding the continuation, modification, or suspension of the trial.

DSMB will be comprised of individuals with relevant clinical expertise and an unblinded biostatistician and also may include pharmacologists, patient advocates, etc.

A DSMB Charter will be developed; it will detail the DSMB's operational procedures and oversight responsibilities including:

- The roles and responsibilities of DSMB members
- The frequency and format of DSMB meetings
- The process for reviewing safety and efficacy data
- The criteria for discontinuing the trial
- The communication plan between the DSMB, the Sponsor, and the IRB.

All DSMB members will disclose any potential conflicts of interest and will be free from significant conflicts that could impact their objectivity. Members with conflicts of interest will recuse themselves from DSMB activities if deemed necessary.

12. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be developed prior to the beginning of participant recruitment that will detail the intended statistical methods that will be used to evaluate the primary, secondary and exploratory endpoints.

12.1. General Considerations

The proposed study is an open-label Phase I investigation intended to gather data on the safety, PK profile and preliminary efficacy of whole organic psilocybin mushrooms in patients suffering from PTSD.

The statistical analysis plan (SAP) will be finalized prior to database lock. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important, primary and secondary, endpoints.

Continuous variables will be summarized by descriptive statistics (number of cases, mean, and standard deviation, median, Q1, Q3, minimum, and maximum). Categorical variables will be summarized using counts of patients and percentages.

All analyses will be performed on patients who were administered the study drug (data on screen failure patients will be listed only).

12.2. Sample Size

A sample size of up to 24 treated participants was selected because it is believed to provide sufficient data to determine whether psilocybin mushrooms are safe for this PTSD patient population.

12.3. Analyses of Safety

Quantitative safety analyses will examine AEs, clinical laboratory parameters, physical examinations, concomitant medications, suicidal ideation, and psychiatric health. All assessments will be presented in data listings.

Treatment-emergent adverse events (TEAEs) are defined as any adverse events that develop

after initiation of treatment, or any event already present that worsens following exposure to treatment.

Number and percentage of patients with TEAE will be summarized by primary system organ class and preferred term. Separate summaries will be done, at minimum, for all TEAEs, serious TEAEs, related TEAEs, severe TEAEs and TEAEs by CTCAE grade.

Continuous parameters will be summarized descriptively by visit including observed values and change from baseline.

12.4. Analyses of Secondary Objectives

Non-compartmental analyses will be used to measure derived PK parameters for psilocin including AUC_{0-t}, $AUC_{0-\infty}$, T_{max} C_{max} and $t_{½}$ (and perhaps others). The PK profile of psilocin will be listed and presented graphically. PK parameters of psilocin will be summarized descriptively.

12.5. Analyses of Exploratory Objectives

The following is an outline of the planned analyses to be done for various exploratory objectives (and associate endpoints).

- Analyses of changes from baseline for continuous questionnaires will be summarized descriptively by visit. and analyzed using repeated measures ANCOVA or generalized linear mixed modeling, as described in the SAP. The statistical significance of the change from baseline ($p<0.05$) will be determined for each measure. 95% confidence intervals will also be derived.
- Change in average sleep duration, sleep latency, sleep efficiency, sleep timing, sleep consistency, nightly heart rate variability, and daily steps from baseline (through product use) will be assessed, as measured by the health tracking wearable device.

  As heart rate and heart rate variability are highly confoundable metrics, analysis of these metrics will be done on all data collected but limited to days without unusual conditions reported by the participants (e.g., unusual alcohol consumption, changes in medication, very high activity, illness, death of a family member or other extraordinary stress unrelated to study participation).

13. ETHICAL CONSIDERATIONS

13.1. Informed Consent

The Investigator is responsible for obtaining informed consent in adherence to Good Clinical Practices (GCP) and according to applicable regulations prior to entering the participant into the clinical trial. Information about events during the course of the study must be given both orally and in writing, in an understandable form. In addition to the explanation of the evaluations, introductory sessions, the risks associated with psilocybin mushrooms self-administration, and the prohibition of the use of psilocybin mushrooms and other medications, and other elements. The information in the informed consent form should note that access to original medical records and processing of coded personal information must be authorized.

The informed consent discussion must be conducted by a person who is qualified, according to applicable local regulations and GCP. The participant should have the opportunity to inquire about details of the study and to consider whether or not to participate.

The ICF must be signed and dated by the participant and must be countersigned by the study site staff member administering the consent process.

Study site staff will provide a copy of the signed ICF to the participant and will maintain the original in the Investigator's study file. During the study, participants will be reminded of upcoming study procedures at each visit to assure their continued comprehension of the ICF.

The written ICF and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised written ICF, and written information, should receive approval from an IRB before use. Written consent to take part in the study session includes giving the Investigator permission to view the participant's recent medical records to assess study eligibility, if needed. Information necessary for study participation includes past medical history, pain evaluation, vital signs, drug and alcohol testing, pregnancy testing, suicide ideation evaluation, and physical examination.

The participant should be informed in a timely manner if new information becomes available that may affect the decision to take part in the study. The communication of this information should be documented.

Participants can withdraw consent for participation in the protocol at any time without prejudice. If a participant withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization or equivalent form, the Investigator will have full access to the participant's medical records, including termination visit information. If a participant revokes only the HIPAA authorization, the Investigator will have full access to all the participants' medical records prior to the date and time of revocation.

The participant also will provide verbal consent to provide confidential information during the pre-screening process, as described in Section 8.1.2.

13.2. Confidentiality of Records

Every effort will be made to strictly safeguard the confidentiality of participants in their role as research participants. Participant contact information logs will be kept on paper at the study sites in locked secure file cabinets. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information.

Despite this, privacy cannot be guaranteed. Except for the screening log, the ICF, and a participant contact information sheet, all patient data will be identified only by the 3-digit screening or 5-digit participant number as a numeric code.

If past medical records are needed, participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. All assessment records will be kept in a locked file drawer or cabinet, and access to measures will be limited to regulatory

agencies, researchers, and individuals analyzing data. Researchers, other than the Investigator, directly involved in the study, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number. Files will be uploaded on a secure computer in a locked office, and only the date of the recording and participant number will be retained in these files.

Maintaining data in a secure environment will prevent the accidental or the deliberate examination of, or removal of data. The Investigator will utilize confidentiality procedures to assure participant privacy. Data to be transferred to remote servers will be encrypted during transfer using a Virtual Private Network.

Clinical trial data will be hosted on an EDC system that is FDA-compliant. All data entered into this system will be de-identified. Participants will only be referred to by numbers and a secondary identifier code. Source records and identifying information will be retained at the study site per GCP. The Investigator will train the study site staff on EDC procedures. Each study staff member with access to the data will be given an individual password.

13.3. Record Retention

The Investigator must retain all study records required by the applicable regulations in a secure and safe facility. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

14. PUBLICATION POLICY

The Investigator recognizes the importance of communicating medical study data and therefore encourages publications in reputable scientific journals and presentations at seminars or conferences. It is understood by the Investigator that the information generated in this study will be used in the development of the product and therefore may be disclosed to government agencies in various countries.

Due regard shall be given to the Investigator's legitimate interests, e.g., manuscript authorship, obtaining optimal patient protection, coordinating and maintaining submissions to health authorities, and coordinating with other ongoing studies in the same field.

The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the clinical trial agreement.

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16. Exhibits

Exhibit 1

Generalized Anxiety Disorder 7 Item Scale (GAD-7)

GAD-7 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Source: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD-PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues. For research information, contact Dr. Spitzer at ris8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission

Scoring GAD-7 Anxiety Severity

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day."
GAD-7 total score for the seven items ranges from 0 to 21.

0–4: minimal anxiety

5–9: mild anxiety

10–14: moderate anxiety

15–21: severe anxiety

Exhibit 2

Life Events Checklist for DSM-5 (LEC-5)

LEC-5 Standard

Instructions: Listed below are a number of difficult or stressful things that sometimes happen to people. For each event check one or more of the boxes to the right to indicate that: (a) it happened to you personally; (b) you witnessed it happen to someone else; (c) you learned about it happening to a close family member or close friend; (d) you were exposed to it as part of your job (for example, paramedic, police, military, or other first responder); (e) you're not sure if it fits; or (f) it doesn't apply to you.

Be sure to consider your *entire life* (growing up as well as adulthood) as you go through the list of events.

Event	Happened to me	Witnessed it	Learned about it	Part of my job	Not sure	Doesn't apply
1. Natural disaster (for example, flood, hurricane, tornado, earthquake)	☐	☐	☐	☐	☐	☐
2. Fire or explosion	☐	☐	☐	☐	☐	☐
3. Transportation accident (for example, car accident, boat accident, train wreck, plane crash)	☐	☐	☐	☐	☐	☐
4. Serious accident at work, home, or during recreational activity	☐	☐	☐	☐	☐	☐
5. Exposure to toxic substance (for example, dangerous chemicals, radiation)	☐	☐	☐	☐	☐	☐
6. Physical assault (for example, being attacked, hit, slapped, kicked, beaten up)	☐	☐	☐	☐	☐	☐
7. Assault with a weapon (for example, being shot, stabbed, threatened with a knife, gun, bomb)	☐	☐	☐	☐	☐	☐
8. Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)	☐	☐	☐	☐	☐	☐
9. Other unwanted or uncomfortable sexual experience	☐	☐	☐	☐	☐	☐
10. Combat or exposure to a war-zone (in the military or as a civilian)	☐	☐	☐	☐	☐	☐
11. Captivity (for example, being kidnapped, abducted, held hostage, prisoner of war)	☐	☐	☐	☐	☐	☐
12. Life-threatening illness or injury	☐	☐	☐	☐	☐	☐
13. Severe human suffering	☐	☐	☐	☐	☐	☐
14. Sudden violent death (for example, homicide, suicide)	☐	☐	☐	☐	☐	☐
15. Sudden accidental death	☐	☐	☐	☐	☐	☐
16. Serious injury, harm, or death you caused to someone else	☐	☐	☐	☐	☐	☐
17. Any other very stressful event or experience	☐	☐	☐	☐	☐	☐

Exhibit 3

PTSD Checklist for DSM-5 (PCL-5)

PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Keeping your worst event in mind, please read each problem carefully and then select one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

Your worst event: _____

In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
2. Repeated, disturbing dreams of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
4. Feeling very upset when something reminded you of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
8. Trouble remembering important parts of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
12. Loss of interest in activities that you used to enjoy?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
13. Feeling distant or cut off from other people?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
15. Irritable behavior, angry outbursts, or acting aggressively?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
16. Taking too many risks or doing things that could cause you harm?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
17. Being "superalert" or watchful or on guard?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
18. Feeling jumpy or easily startled?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
19. Having difficulty concentrating?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
20. Trouble falling or staying asleep?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯

Exhibit 4

Patient Health Questionnaire-9 (PHQ -9)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

ID #: _____ **DATE:** _____

Over the last 2 *weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

A2663B 10-04-2005

Exhibit 5

Healing Experience of All Life Stressors (NIH HEALS)

Last revised 04/02/2018_RA Date: Number:
NIH-HEALS

Below is a list of statements. By circling **one number per question**, please indicate how much you agree with each statement as it applies to you since your life changing experience(s) such as losses i.e. death, divorce, physical disability, serious/life limiting illness, traumatic events, or any other life altering experiences. There is no right or wrong answer to these statements. Your response is based on your unique experiences, so it may not reflect responses of others.

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
1. I am content with my life.	1	2	3	4	5
2. I have a sense of purpose in my life.	1	2	3	4	5
3. The connection with a higher power is important to me.	1	2	3	4	5
4. I gain awareness from self-reflection.	1	2	3	4	5
5. I enjoy activities that involve both mind/ body such as meditation, prayer, yoga, tai chi, chanting.	1	2	3	4	5
6. I feel isolated.	1	2	3	4	5
7. I feel calm even though I am not in control of my situation.	1	2	3	4	5
8. I accept things that I cannot change.	1	2	3	4	5
9. Working through thoughts about the possibility of dying brought meaning to my life.	1	2	3	4	5
10. Difficult circumstances in my life have increased my compassion towards others.	1	2	3	4	5
11. I want to make the most of my life.	1	2	3	4	5
12. I survive difficult circumstances because of a higher power.	1	2	3	4	5
13. My situation strengthened my connection to a higher power.	1	2	3	4	5

Below is a list of statements. By circling **one number per question**, please indicate how much you agree with each statement as it applies to you since your life changing experience(s) such as losses i.e. death, divorce, physical disability, serious/life limiting illness, traumatic events, or any other life altering experiences. There is no right or wrong answer to these statements. Your response is based on your unique experiences, so it may not reflect responses of others.

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
14. My religious beliefs help me feel calm when faced with difficult circumstances in life.	1	2	3	4	5
15. My personal religious practice is important to me.	1	2	3	4	5
16. My participation in a religious community is an important aspect of my life.	1	2	3	4	5
17. I get support from my religious community.	1	2	3	4	5
18. My religious beliefs give me hope.	1	2	3	4	5
19. Doing something I am passionate about gives me purpose during difficult times (e.g. work, hobbies, volunteering, my religious institution, reading groups).	1	2	3	4	5
20. I find meaning in helping others.	1	2	3	4	5
21. Connection with my family has become my highest priority.	1	2	3	4	5
22. Support from my family lifts my spirits, which gives me hope during difficult times in life.	1	2	3	4	5
23. I am not getting the support I need.	1	2	3	4	5
24. I am confident that my medical caregivers will respond to my needs.	1	2	3	4	5

Last revised 04/02/2018_RA Date: Number:
NIH-HEALS

Below is a list of statements. By circling **one number per question**, please indicate how much you agree with each statement as it applies to you since your life changing experience(s) such as losses i.e. death, divorce, physical disability, serious/life limiting illness, traumatic events, or any other life altering experiences. There is no right or wrong answer to these statements. Your response is based on your unique experiences, so it may not reflect responses of others.

	Strongly Disagree	Disagree	Neither Agree or Disagree	Agree	Strongly Agree
25. My friends provide the support I need during difficult times.	1	2	3	4	5
26. I seek more of a connection in my relationships.	1	2	3	4	5
27. I take more time to be in the moment.	1	2	3	4	5
28. My experience with multiple losses has made it hard to be hopeful during difficult times (such as death, divorce, competency, physical disability).	1	2	3	4	5
29. Working through my own grief has brought meaning to my life.	1	2	3	4	5
30. I have a sense of peace in my life.	1	2	3	4	5
31. I have an increased sense of gratitude.	1	2	3	4	5
32. Being surrounded by nature is meaningful.	1	2	3	4	5
33. Creative arts bring peace to my life.	1	2	3	4	5
34. Life challenges interfere with activities that are important to me.	1	2	3	4	5
35. Life challenges raised my desire to be more positive.	1	2	3	4	5

Exhibit 6

Brief Pain Inventory (BPI)

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

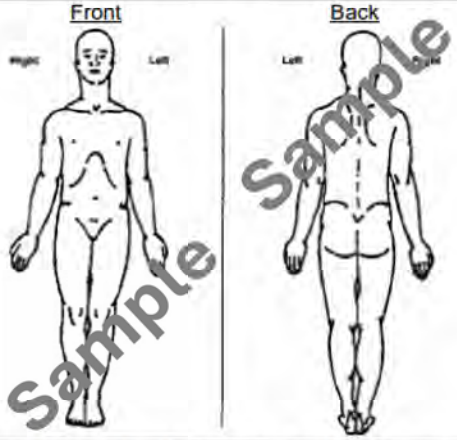
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Exhibit 7

Columbia-Suicide Severity Rating Scale (C-SSRS)

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 thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** 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 thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about 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 thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** 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."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** 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 decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature 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?*** ***Write response*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

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. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, 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** ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (but 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 make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt or Self-Interrupted 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 himself/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted or self-interrupted _____
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 done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of preparatory acts _____
Suicide: Death by suicide occurred since last assessment.	**Yes** ☐ **No** ☐
	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* _____

Exhibit 8

Profile of Mood States (POMS)

PROFILE OF MOOD STATES (POMS) QUESTIONNAIRE

Baseline Survey

Please complete the following questions **BEFORE** you complete the meditation demonstration:

Role: ☐ Attending ☐ Fellow ☐ Resident ☐ Administrative Staff ☐ Other:_____

Gender: ☐ Male ☐ Female ☐ I prefer not to answer

Age: ☐ 20-40 ☐ 40-60 ☐ > 60 ☐ I prefer not to answer

Years of Service: ☐ 0-5 ☐ 5-10 ☐ 10-20 ☐ > 20 ☐ I prefer not to answer

Meditated 3-4 times a week before: ☐ Yes ☐ No ☐ I prefer not to answer

Aerobic exercises 3-4 time[illegible] week: ☐ Yes ☐ No ☐ I prefer not to answer

Below is a list of words that describe feelings people have. Please **CHECK THE BOX THAT BEST DESCRIBES HOW YOU FEEL RIGHT NOW**.

	Not At All	A Little	Moderately	Quite a lot	Extremely
Tense					
Angry					
Worn Out					
Unhappy					
Proud					
Lively					
Confused					
Sad					
Active					
On-edge					
Grouchy					

	Not At All	A Little	Moderately	Quite a lot	Extremely
Ashamed					
Energetic					
Hopeless					
Uneasy					
Restless					
Unable to concentrate					
Fatigued					
Competent					
Annoyed					
Discouraged					
Resentful					
Nervous					
Miserable					
Confident					
Bitter					
Exhausted					
Anxious					
Helpless					
Weary					
Satisfied					
Bewildered					
Furious					
Full of Pep					
Worthless					
Forgetful					
Vigorous					
Uncertain about things					
Bushed					
Embarrassed					

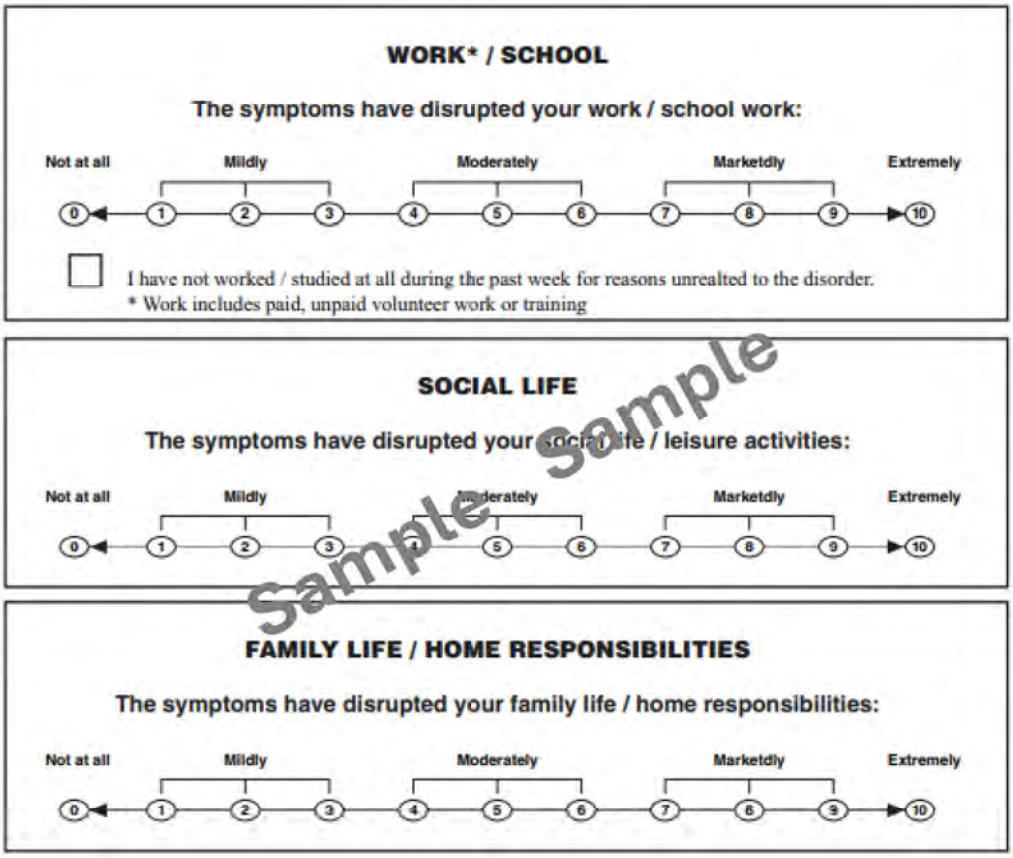
Exhibit 9

Sheehan Disability Scale (SDS)

Sheehan Disability Scale

A brief, patient rated, measure of disability and impairment.

Please mark ONE circle for each scale.



Days Lost

On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

Days Unproductive

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced? _____

Exhibit 10

Watts Connectedness Scale (WCS)

Watts Connectedness Scale (WCS)

Reference

Watts' et al.

Instructions

Reflecting on how you have felt over the past 2 weeks, please rate the following items on a scale from **'Not at all' to 'Entirely'** according to how you have felt over this time period. Please answer every item, even if you are unsure or feel the item is unclear or poorly worded. Drag the indicator to a position on the scale that shows how much you agree or disagree with each of the following statements.

Response format

Each item is rated on a 0 – 100 visual analogue scale with the anchors 0 = Not at all, 100 = Entirely

Final items

1. *I have felt trapped in my mind.*
2. *My mind has felt connected to my heart/emotion.*
3. *I have felt connected to my senses (touch, taste, sight smell, hearing).*
4. *I have felt connected to a range of emotions.*
5. *If I had chosen to, I could have 'sat with' painful memories.*
6. *I have felt connected to my body.*
7. *I have been able to fully experience emotion, whether positive or negative.*
8. *I have felt alone.*
9. *I have felt connected to friends and/or family.*
10. *I have felt connected to a community.*
11. *I have felt connected to all humanity.*
12. *I have felt unwelcome amongst others.*
13. *I have felt separate from the world around me.*
14. *I have felt connected to a purpose in life.*
15. *I have felt connected to nature.*
16. *I have felt connected to a spiritual essence (in the secular or religious sense).*
17. *I have felt connected to a source of universal love.*
18. *I have seen things from a broad perspective, 'the bigger picture'.*
19. *I have felt that everything is interconnected.*

Exhibit 11

Mystical Experience Questionnaire (MEQ30) – Revised

mystical experience questionnaire (meq30)

instructions: looking back on the entirety of your psychedelic session, please rate the degree to which at any time during that session you experienced the following phenomena. Answer each question according to your feelings, thoughts, and experiences at the time of the psychedelic session. In making each of your ratings, use the following scale: ***0*** *none/not at all;* ***1*** *so slight cannot decide;* ***2*** *slight;* ***3*** *moderate;* ***4*** *strong (equivalent in degree to any other strong experience);* ***5*** *extreme (more than any other time in my life and stronger than* ***4****).* Feel free to use *'half-point in-between scores'* if these are applicable.

		0	1	2	3	4	5
1	Loss of your usual sense of time. *(T)*						
2	Experience of amazement. *(P)*						
3	Sense that the experience cannot be described adequately in words. *(I)*						
4	Gain of insightful knowledge experienced at an intuitive level						
5	Feeling that you experienced eternity or infinity.						
6	Experience of oneness or unity with the objects and/or persons perceived in your surroundings.						
7	Loss of your usual sense of space. *(T)*						
8	Feelings of tenderness and gentleness. *(P)*						
9	Certainty of encounter with ultimate reality (in the sense of being able to 'know' and 'see' what is really real at some point during your experience).						
10	Feeling that you could not do justice to your experience by describing it in words. *(I)*						
11	Loss of your usual sense of where you were. *(T)*						
12	Feelings of peace and tranquillity. *(P)*						
13	Sense of being 'outside of' time, beyond past and future. *(T)*						
14	Freedom from the limitations of your personal self and feeling of unity or bond with what was felt to be greater than your personal self.						
15	Sense of being at a spiritual height.						
16	Experience of pure being and pure awareness (beyond the world of sense impressions).						
17	Experience of ecstasy. *(P)*						
18	Experience of the insight that "all is One".						
19	Being in a realm with no space boundaries. *(T)*						
20	Experience of oneness in relation to an "inner world" within.						
21	Sense of reverence.						
22	Experience of timelessness. *(T)*						
23	You are convinced now, as you look back on your experience, that in it you encountered ultimate reality (that you 'knew' and 'saw' what was really real).						
24	Feeling that you experienced something profoundly sacred and holy.						
25	Awareness of the life or living presence in all things.						
26	Experience of the fusion of your personal self into a larger whole.						
27	Sense of awe or awesomeness. *(P)*						
28	Experience of unity with ultimate reality.						
29	Feeling that it would be difficult to communicate your own experience to others who have not had similar experiences. *(I)*						
30	Feelings of joy. *(P)*						

Exhibit 12

Challenging Experience Questionnaire (CEQ)

Instructions: Looking back on the entirety of your session, please rate the degree to which at any time during that session you experienced the following phenomena. Answer each question according to your feelings, thoughts, and experiences at the time of the session. In making each of your ratings, use the following scale:

0 – none; not at all

1 – so slight cannot decide

2 – slight

3 – moderate

4 – strong

5 – extreme (more than ever before in my life)

_____ 1. Isolation and loneliness

_____ 2. Sadness

_____ 3. Feeling my heart beating

_____ 4. I had the feeling something horrible would happen

_____ 5. Feeling my body shake/tremble

_____ 6. Feelings of grief

_____ 7. Experience of fear

_____ 8. Fear that I might lose my mind or go insane

_____ 9. I felt like crying

_____ 10. Feeling of isolation from people and things

_____ 11. Feelings of despair

_____ 12. I had the feeling that people were plotting against me

_____ 13. I was afraid that the state I was in would last forever

_____ 14. Anxiousness

_____ 15. I felt shaky inside

_____ 16. I had the profound experience of my own death

_____ 17. I felt my heart beating irregularly or skipping beats

_____ 18. Pressure or weight in my chest or abdomen

_____ 19. I experienced a decreased sense of reality

_____ 20. I felt as if I was dead or dying

_____ 21. Panic

_____ 22. Experience of antagonism toward people around me

_____ 23. Despair

_____ 24. I felt isolated from everything and everyone

_____ 25. Emotional and/or physical suffering

_____ 26. I felt frightened

Exhibit 13

5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)

5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)

A. Dittrich, D. Lamparter, M. Maurer

Translation from the original German by Felix Hasler and Rael Cahn

Instructions

On the following pages you will find a number of statements and below each statement a line with the endpoints "**No**, not more than usually" and "**Yes**, much more than usually." The line represents something like a thermometer that will be used to assess alterations from your normal waking consciousness.

Please rate to what extent the statements apply to your particular experience – compared to normal waking consciousness – by making a vertical mark on the line below the statements.

Please note that your normal waking consciousness corresponds to a mark at the very left end of the scale, i.e.: "No, not more than usually."

Example:

I felt elated.

No, not more than usually ——— **Yes**, much more than usually

Please use all intermediate gradations to most accurately describe your experience.

1. I felt that I was in a wonderful other world.

No, not more than usually — **Yes**, much more than usually

2. My thoughts and actions were slowed down.

No, not more than usually — **Yes**, much more than usually

3. Bodily sensations were very enjoyable.

No, not more than usually — **Yes**, much more than usually

4. I heard single words without knowing where they came from.

No, not more than usually — **Yes**, much more than usually

5. I heard rings and tones without knowing where they came from.

No, not more than usually — **Yes**, much more than usually

6. I felt as if dark forces had overtaken me.

No, not more than usually — **Yes**, much more than usually

7. I saw things I knew were not real.

No, not more than usually — **Yes**, much more than usually

8. I felt like a puppet or marionette.

No, not more than usually — **Yes**, much more than usually

9. I felt connected to a higher power.

No, not more than usually — **Yes**, much more than usually

10. I felt sleepy.

No, not more than usually — **Yes**, much more than usually

11. A melody occured to me that I had to constantly repeat.

No, not more than usually — **Yes**, much more than usually

12. I experienced boundless pleasure.

No, not more than usually — **Yes**, much more than usually

13. Meaningless noises sounded like real words or phrases.

No, not more than usually — **Yes**, much more than usually

14. I saw regular patterns with closed eyes or in complete darkness.

No, not more than usually — **Yes**, much more than usually

15. I felt drunk.

No, not more than usually — **Yes**, much more than usually

16. I felt I was being transformed forever in a miraculous way.

No, not more than usually — **Yes**, much more than usually

17. I felt that I was on the verge of unconsciousness.

No, not more than usually — **Yes**, much more than usually

18. Everything seemed to unify into a oneness.

No, not more than usually — **Yes**, much more than usually

19. I heard my thoughts as if I had spoken them out loud.

No, not more than usually — **Yes**, much more than usually

20. Sounds seemed to influence what I saw.

No, not more than usually — **Yes**, much more than usually

21. I felt tormented.

No, not more than usually — **Yes**, much more than usually

22. I saw colors with closed eyes or in complete darkness.

No, not more than usually — **Yes**, much more than usually

23. Shapes seemed to be changed by sounds or noises.

No, not more than usually — **Yes**, much more than usually

24. I perceived everything as blurry, as if through a kind of fog.

No, not more than usually — **Yes**, much more than usually

25. A voice commented on everything I thought although no one was there.

No, not more than usually — **Yes**, much more than usually

26. I felt as if I no longer had a body.

No, not more than usually — **Yes**, much more than usually

27. I felt incapable of making even the smallest decision.

No, not more than usually — **Yes**, much more than usually

28. Some everyday things acquired special meaning.

No, not more than usually — **Yes**, much more than usually

29. I felt drowsy.

No, not more than usually — **Yes**, much more than usually

30. I heard complete sentences without knowing where they came from.

No, not more than usually — **Yes**, much more than usually

31. Things in my environment had a new strange meaning.

No, not more than usually — **Yes**, much more than usually

32. I was afraid that the state I was in would last forever.

No, not more than usually — **Yes**, much more than usually

33. I saw brightness or flashes of light with closed eyes or in complete darkness.

No, not more than usually — **Yes**, much more than usually

34. I felt one with my surroundings.

No, not more than usually — **Yes**, much more than usually

35. Worries and anxieties of everyday life felt unimportant.

No, not more than usually — **Yes**, much more than usually

36. My sense of time and space was altered as if I was dreaming.

No, not more than usually — **Yes**, much more than usually

37. My perception was blurred.

No, not more than usually — **Yes**, much more than usually

38. I had difficulties in distinguishing important from unimportant.

No, not more than usually — **Yes**, much more than usually

39. I saw whole scenes roll by with closed eyes or in complete darkness.

No, not more than usually — **Yes**, much more than usually

40. I felt extraordinary powers within myself.

No, not more than usually — **Yes**, much more than usually

41. I experienced a touch of eternity.

No, not more than usually — **Yes**, much more than usually

42. Conflicts and contradictions seemed to dissolve.

No, not more than usually — **Yes**, much more than usually

43. I was scared without knowing exactly why.

No, not more than usually — **Yes**, much more than usually

44. I experienced everything as frighteningly distorted.

No, not more than usually — **Yes**, much more than usually

45. The world seemed to me beyond good and evil.

No, not more than usually — **Yes**, much more than usually

46. I experienced my surroundings as strange and weird.

No, not more than usually — **Yes**, much more than usually

47. I felt as if I were paralyzed.

No, not more than usually — **Yes**, much more than usually

48. I heard music without knowing where it came from.

No, not more than usually — **Yes**, much more than usually

49. heard something faintly that I could not identify.

No, not more than usually — **Yes**, much more than usually

50. I felt very profound.

No, not more than usually — **Yes**, much more than usually

51. I felt numb.

No, not more than usually — **Yes**, much more than usually

52. I experienced past, present, and future as a oneness.

No, not more than usually — **Yes**, much more than usually

53. I experienced unbearable emptiness.

No, not more than usually — **Yes**, much more than usually

54. Objects in my surroundings engaged me emotionally much more than usual.

No, not more than usually — **Yes**, much more than usually

55. From an initially diffuse noise, which I could not identify as real, clear rings and tones evolved.

No, not more than usually — **Yes**, much more than usually

56. I felt threatened.

No, not more than usually — **Yes**, much more than usually

57. Many things appeared to me as breathtakingly beautiful.

No, not more than usually — **Yes**, much more than usually

58. Things came to my mind that I thought long forgotten.

No, not more than usually — **Yes**, much more than usually

59. I felt like I do shortly before falling asleep.

No, not more than usually — **Yes**, much more than usually

60. My body felt numb, lifeless, and/or alien.

No, not more than usually — **Yes**, much more than usually

61. I felt as if I was half-asleep.

No, not more than usually — **Yes**, much more than usually

62. I had the impression I was out of my body.

No, not more than usually ——— **Yes**, much more than usually

63. I felt as if I was floating.

No, not more than usually ——— **Yes**, much more than usually

64. I felt isolated from everything and everyone.

No, not more than usually ——— **Yes**, much more than usually

65. I heard voices that did not come from the surroundings as usual.

No, not more than usually ——— **Yes**, much more than usually

66. I heard something like a buzzing, swooshing, or humming without recognizing the cause.

No, not more than usually ——— **Yes**, much more than usually

67. I was not able to complete a thought; my thoughts repeatedly became disconnected.

No, not more than usually ——— **Yes**, much more than usually

68. I felt I was about to fall asleep.

No, not more than usually ——— **Yes**, much more than usually

69. I had insights into connections that had previously puzzled me.

No, not more than usually — **Yes**, much more than usually

70. Many things seemed incredibly funny to me.

No, not more than usually — **Yes**, much more than usually

71. The boundaries between myself and my surroundings seemed to blur.

No, not more than usually — **Yes**, much more than usually

72. I could see images from my memory or imagination with extreme clarity.

No, not more than usually — **Yes**, much more than usually

73. I felt totally free and released from all obligations.

No, not more than usually — **Yes**, much more than usually

74. I heard diffuse noises without knowing where they came from.

No, not more than usually — **Yes**, much more than usually

75. The colors of things seemed to be altered by sounds or noises.

No, not more than usually — **Yes**, much more than usually

76. Sounds and noises were fainter than usual.

No, not more than usually — **Yes**, much more than usually

77. I had very original thoughts.

No, not more than usually — **Yes**, much more than usually

78. I had the feeling that I no longer had my own will.

No, not more than usually — **Yes**, much more than usually

79. I was afraid of losing control over myself.

No, not more than usually — **Yes**, much more than usually

80. I stayed frozen in an very unnatural position for an extended period of time.

No, not more than usually — **Yes**, much more than usually

81. I experienced a kind of awe.

No, not more than usually — **Yes**, much more than usually

82. My imagination was extremely vivid.

No, not more than usually — **Yes**, much more than usually

83. Things in my surroundings appeared smaller or larger.

No, not more than usually — **Yes**, much more than usually

84. I felt exhausted.

No, not more than usually — **Yes**, much more than usually

85. Time passed slowly in a tormenting way.

No, not more than usually — **Yes**, much more than usually

86. I experienced profound inner peace.

No, not more than usually — **Yes**, much more than usually

87. Everything around me seemed to be animated with life.

No, not more than usually — **Yes**, much more than usually

88. Everything happened so fast that I could not follow it all.

No, not more than usually — **Yes**, much more than usually

89. I had the feeling that something terrible was going to happen.

No, not more than usually — **Yes**, much more than usually

90. I was able to remember certain events with exceeding clarity.

No, not more than usually — **Yes**, much more than usually

91. I experienced an all-embracing love.

No, not more than usually — **Yes**, much more than usually

92. There were sounds in the room that I feel were unlikely to have been real.

No, not more than usually — **Yes**, much more than usually

93. I heard a ticking, knocking, ringing, or rattling without being able to recognize the cause.

No, not more than usually — **Yes**, much more than usually

94. My experience had religious aspects to it.

No, not more than usually — **Yes**, much more than usually

Exhibit 14

Alcohol Use Disorders Identification Test (AUDIT)

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?
   (0) Never [Skip to Qs 9-10]
   (1) Monthly or less
   (2) 2 to 4 times a month
   (3) 2 to 3 times a week
   (4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   (0) 1 or 2
   (1) 3 or 4
   (2) 5 or 6
   (3) 7, 8, or 9
   (4) 10 or more

3. How often do you have six or more drinks on one occasion?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
   Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4. How often during the last year have you found that you were not able to stop drinking once you had started?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?
   (0) No
   (2) Yes, but not in the last year
   (4) Yes, during the last year

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?
    (0) No
    (2) Yes, but not in the last year
    (4) Yes, during the last year

Record total of specific items here

If total is greater than recommended cut-off, consult User's Manual.

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

Exhibit 15

Drug Use Disorders Identification Test (DUDIT)

Id. nr. _____

DUDIT Drug Use Disorders Identification Test

Here are a few questions about drugs. Please answer as correctly and honestly as possible by indicating which answer is right for you.

☐ Man ☐ Woman Age ____

1. How often do you use drugs other than alcohol? (See list of drugs on back side.)	Never ☐	Once a month or less often ☐	2-4 times a month ☐	2-3 times a week ☐	4 times a week or more often ☐
2. Do you use more than one type of drug on the same occasion?	Never ☐	Once a month or less often ☐	2-4 times a month ☐	2-3 times a week ☐	4 times a week or more often ☐
3. How many times do you take drugs on a typical day when you use drugs?	0 ☐	1-2 ☐	3-4 ☐	5-6 ☐	7 or more ☐
4. How often are you influenced heavily by drugs?	Never ☐	Less often than once a month ☐	Every month ☐	Every week ☐	Daily or almost every day ☐
5. Over the past year, have you felt that your longing for drugs was so strong that you could not resist it?	Never ☐	Less often than once a month ☐	Every month ☐	Every week ☐	Daily or almost every day ☐
6. Has it happened, over the past year, that you have not been able to stop taking drugs once you started?	Never ☐	Less often than once a month ☐	Every month ☐	Every week ☐	Daily or almost every day ☐
7. How often over the past year have you taken drugs and then neglected to do something you should have done?	Never ☐	Less often than once a month ☐	Every month ☐	Every week ☐	Daily or almost every day ☐
8. How often over the past year have you needed to take a drug the morning after heavy drug use the day before?	Never ☐	Less often than once a month ☐	Every month ☐	Every week ☐	Daily or almost every day ☐
9. How often over the past year have you had guilt feelings or a bad conscience because you used drugs?	Never ☐	Less often than once a month ☐	Every month ☐	Every week ☐	Daily or almost every day ☐
10. Have you or anyone else been hurt (mentally or physically) because you used drugs?		No ☐	Yes, but not over the past year ☐		Yes, over the past year ☐
11. Has a relative or a friend, a doctor or a nurse, or anyone else, been worried about your drug use or said to you that you should stop using drugs?		No ☐	Yes, but not over the past year ☐		Yes, over the past year ☐

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Turn the page to see the list of drugs

LIST OF DRUGS

(Note! Not alcohol!)

Cannabis	Amphetamines	Cocaine	Opiates	Hallucinogens	Solvents/inhalants	GHB and others
Marijuana Hash Hash oil	Methamphetamine Phenmetraline Khat Betel nut Ritaline (Methylphenidate)	Crack Freebase Coca leaves	Smoked heroin Heroin Opium	Ecstasy LSD (Lisergic acid) Mescaline Peyote PCP, angel dust (Phencyclidine) Psilocybin DMT (Dimethyltryptamine)	Thinner Trichlorethylene Gasoline/petrol Gas Solution Glue	GHB Anabolic steroids Laughing gas (Halothane) Amyl nitrate (Poppers) Anticholinergic compounds

PILLS – MEDICINES

Pills count as drugs when you take

- more of them or take them more often than the doctor has prescribed for you
- pills because you want to have fun, feel good, get "high", or wonder what sort of effect they have on you
- pills that you have received from a relative or a friend
- pills that you have bought on the "black market" or stolen

SLEEPING PILLS/SEDATIVES

Alprazolam	Glutethimide	Rohypnol
Amobarbital	Halcion	Secobarbital
Apodorm	Heminevrin	Sobril
Apozepam	Iktorivil	Sonata
Aprobarbital	Imovane	Stesolid
Butabarbital	Mephobarbital	Stilnoct
Butalbital	Meprobamate	Talbutal
Chloral hydrate	Methaqualone	Temesta
Diazepam	Methohexital	Thiamyal
Dormicum	Mogadon	Thiopental
Ethcholorvynol	Nitrazepam	Triazolam
Fenemal	Oxascand	Xanor
Flunitrazepam	Pentobarbital	Zopiklon
Fluscand	Phenobarbital	

PAINKILLERS

Actiq	Durogesic	OxyNorm
Coccilana-Etyfin	Fentanyl	Panocod
Citodon	Ketodur	Panocod forte
Citodon forte	Ketogan	Paraflex comp
Dexodon	Kodein	Somadril
Depolan	Maxidon	Spasmofen
Dexofen	Metadon	Subutex
Dilaudid	Morfin	Temgesic
Distalgesic	Nobligan	Tiparol
Dolcontin	Norflex	Tradolan
Doleron	Norgesic	Tramadul
Dolotard	Opidol	Treo comp
Doloxene	OxyContin	

Pills do NOT count as drugs if they have been prescribed by a doctor and you take them in the prescribed dosage.