Study Protocol

The Safety, Tolerability, and Initial Efficacy of Psilocybin in Participants with Anorexia Nervosa

Form Version Date: March 10, 2022
IRB Approval Date: March 23, 2022

NCT04661514

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 03/10/2022

1. PROJECT TITLE

The Safety, Tolerability, and Initial Efficacy of Psilocybin in Participants with Anorexia Nervosa

2. PRINCIPAL INVESTIGATOR

Walter Kaye, MD

3. FACILITIES

Altman Clinical and Translation Research Institute (ACTRI)

4. ESTIMATED DURATION OF THE STUDY

We expect to begin enrolling participants in April 2021. The estimated duration of the study is 1 year.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Psilocybin is a controlled drug and a chemical compound found in some species of mushrooms. Recent studies have suggested that psilocybin may help in treating psychiatric illnesses and we wish to investigate this further in anorexia nervosa (AN). Psilocybin works on the serotonin system in the brain. Considerable evidence points to alterations in the serotonin system in AN, which contribute to dysregulation of mood, appetite, motivation and impulse control. Individuals with AN tend towards having increased binding of 5HT1A receptors, a decreased binding of the 5HT2Areceptor, as well as altered endogenous brain 5HT secretion. Since psilocybin's mechanism of action is mediated by serotonin 2A (5-HT2A) receptor agonism,[18] this supports the possibility that this drug might reverse AN symptoms. The main purpose of this study is to test the safety and tolerability and feasibility of psilocybin in AN, and how well it works to lessen AN symptoms. We will do this by administering a single dose of 25 mg of psilocybin along with psychotherapeutic support up to 20 participants with a diagnosis of AN. AN symptoms will be measured by a change in the score of questionnaires that evaluate eating disorder symptoms by having participants complete interviews and questionnaires before the dosing, and at Day 1, Week 1, Week 4, and Week 12 after the dose. Additional information about the subjects' eating disorder symptoms, and other psychosocial symptoms will also be collected during the study.

6. SPECIFIC AIMS

This study aims to establish the safety, tolerability and feasibility of psilocybin in adult patients with AN, as well as gather pilot data on possible efficacy via the following objectives. It is hoped that the results of this study will form the basis for a Randomized Control Trial with a suitable control condition to test the efficacy of this treatment in AN.

Primary Objective: To evaluate the safety and tolerability of one 25mg dose of psilocybin in participants with AN based on adverse events (AEs), changes in vital signs, electrocardiograms (ECGs), clinical laboratory tests, and suicidality.

Secondary Objectives:

The secondary objectives are to explore the efficacy of 25mg psilocybin on eating disorder symptoms and behaviours, body image, anxiety, food related obsessions and rituals, and body weight.

Exploratory Objective:

The exploratory objectives are to explore the effects of 25mg psilocybin on psychosocial impairment, depressive symptoms, motivational states and appetitive states including hunger and fullness and desire to eat. Links between psychedelic intensity and changes in efficacy variables will also be explored, as well as patient experience and acceptability of the treatment.

7. BACKGROUND AND SIGNIFICANCE

Psilocybin belongs to a class of drugs referred to as psychedelics ('mind-manifesting'). Specifically, psilocybin is considered a 5-hydroxytryptaminergic (serotonergic) psychedelic, along with other tryptamines such as

dimethyltryptamine (DMT), ergolines such as lysergic acid diethylamide (LSD), and phenethylamines such as mescaline. Psilocybin was first isolated from psilocybe mushrooms by Hofmann in 1957, and later synthesized by him in 1958. Psilocybin has been used in psychiatric research and in psychodynamic orientated psychotherapy from the early to mid-1960s up until it became a Schedule 1 substance in the United States (US) in 1970, and until the 1980s in Germany. Research on the effects of psilocybin resumed in the mid-1990s, and it is currently the preferred compound for use in clinical research of 5-hydroxytryptaminergic psychedelics because it has a shorter duration of action and suffers from less notoriety and stigma than other similar drugs.

Study Rationale

Because there are no proven treatments that normalize core symptoms in adult AN, a disorder with high chronicity and mortality, many individuals seek out alternative approaches to care. Recent evidence has suggested that anxiety,[1] OCD, and diminished reward or motivation[2] play key roles in the development and maintenance of dysfunctional eating,[3-6] and poor outcome.[7] Anti-anxiety medications, such as benzodiazepines are not effective in AN.[8] Furthermore, currently available behavioral and pharmacological treatments have not proven to be effective in producing clinically significant changes in weight and eating disorder symptoms.[9-14] A subset of those with AN develop a chronic course associated with high morbidity and mortality.[9, 10]

Considerable evidence suggests that altered brain serotonin (5-HT) function contributes to dysregulation of appetite, mood, motivation, and impulse control in AN.[15] Individuals with AN tend to have increased binding of the 5HT1A receptor and decreased binding of the 5HT2A receptor as well as altered endogenous brain 5HT secretion.[16, 17] Psilocybin is a psychedelic whose mechanism of action is mediated by serotonin 2A (5-HT2A) receptor agonism,[18] supporting the possibility that this drug might reverse AN symptoms. Psilocybin may represent a promising new treatment for AN. However, no studies have tested psilocybin in this eating disorder population. Accordingly, this study aims to establish the safety, tolerability and dosing of psilocybin in adult patients with AN, as well as gather pilot data on possible efficacy.

In recent years, a growing number of studies have demonstrated the efficacy and safety of psilocybin in clinical trials for a range of psychiatric illnesses. These include: treatment resistant depression, obsessive compulsive disorder, addiction, and anxiety (in particular end of life anxiety). Whilst there have been no completed trials to date of psilocybin for AN, a study with ceremonial ayahuasca (another classical psychedelic) found evidence of a reduction in eating disordered symptoms following ayahuasca. In addition, many patients with AN have comorbid anxiety, depression and obsessive compulsive disorder.

Pharmacokinetics

Psilocybin is detectable in plasma 20 to 40 min after oral administration of 0.224 mg/kg (10-20 mg total dose). Orally ingested psilocybin is metabolised (dephosphorylated) in the liver, and primarily transformed into the active hydroxy metabolite, psilocin. Psilocybin is detectable in plasma 30 min after administration and psilocin is detectable in plasma 15 to 50 min after oral administration of 0.2 mg/kg psilocybin. Therefore, psilocybin is essentially a prodrug and psilocin represents the pharmacologically active agent in systemic circulation. The elimination half-life of psilocybin is 50 min. Psilocin's half-life ranges between 2 and 3 h, and is detectable 6 h after oral administration. Hasler et al. and Lindenblatt et al. reported similar but not identical findings, with peak levels of psilocin appearing between 80 to 105 min and psilocin half-life ranging between 2.25 h for 0.2 mg/kg and 2.7 h for 0.22 mg/kg. The majority, 80%, of psilocin in plasma was found to be in a conjugated form. Both psilocin (at 90-97%) and psilocybin (3-10%) are detectable in human urine, unmodified (only 3-10%) and particularly conjugated with glucuronic acid. The majority of psilocin recovered in urine is excreted within 3 h after oral administration and is completely eliminated from the body within 24 hours.

Preclinical Pharmacology

Psilocybin and its active metabolite psilocin directly affect a number of 5-HT receptor subtypes without directly affecting other neurotransmitter systems.

Human psilocybin research has confirmed the importance of 5-HT_{2A} stimulation for the psychedelic effects of psilocybin

and psilocin as the effects can be blocked by a 5-HT_{2A} receptor antagonist. Reviews of the pharmacology of psilocybin is provided by Passie, and more current knowledge and perspective by Tyls et al.

When assessed for potential effects on the human-ether-à-go-go related gene channel psilocybin was shown to be without significant effects when tested up to concentrations of 1 mM.

Although the literature on the effect of psilocin at the 5-HT_{2B} is somewhat contradictory, the most recent publication by Rickli et al. indicates that the half-maximal effective concentration (EC_{50}) for activation of the 5-HT_{2B} receptor is greater than 20 μM. That concentration would generally be considered to be pharmacologically inactive *in vivo* because plasma concentrations would never reach 20 μM or greater after a single administration of psilocin. Brown et al. indicate that the maximal plasma concentration achieved after a single dose of 0.45 mg/kg in normal humans would not reach 200 nM (0.2 μM). In any event, all studies suggest that chronic activation of the 5-HT_{2B} is necessary in order to invoke cardiac valvulopathy, and with a single administration there should be no concern for that effect. With the EC_{50} reported by Rickli et al., even multiple administrations of psilocin would not be expected to be harmful. The valvulopathy induced by Fen-phen, or ergoline type anti-Parkinson agents, involved daily administration of the drugs over a significant period of time. Thus, there is no expectation that single use of psilocybin will be problematic.

Clinical Adverse Event Profile

The use of psilocybin in psychotherapy have been reported since the 1960's, but these studies suffer from a lack of experimental control and standardised assessments. Owing to the absence of adequate control groups, and use of follow-up measurements with vague criteria for therapeutic outcomes, the studies do not clearly distinguish between the drug or the therapeutic engagement itself that produced the reported beneficial effect.

The safety of psilocybin should be considered in terms of benefit and risk. Within the context of psilocybin administration in a controlled setting, a participant may report visual or auditory disturbances, feelings of unreality, altered sense of time, and other changes in mood or affect amongst other neuropsychiatric observations which have been previously described (see Table 4.1 of the current Psilocybin IB). These effects are both expected, and may be a necessary component of therapeutic response. Investigators must follow regulatory guidance under 21 CFR 312.32(a) for AE reporting which addresses untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

Dosing Regimen

The choice of the dose for this study (25mg) was based on previous studies. Carhart-Harris successfully evaluated 2 oral doses of psilocybin (10 mg and 25 mg) administered 7 days apart to patients with unipolar treatment-resistant depression; and minimal AEs were reported in this study. Work by the Griffiths group showed that under supportive conditions, psilocybin at doses of 20 to 30 mg/70 kg can dose-dependently occasion mystical-type experiences. The 25mg dose will be administered under supportive conditions, and as detailed, this dose falls well within the safe and tolerable range. All participants will meet medical stability inclusion and exclusion criteria as detailed in this protocol.

8. PROGRESS REPORT

N/A

9. RESEARCH DESIGN AND METHODS

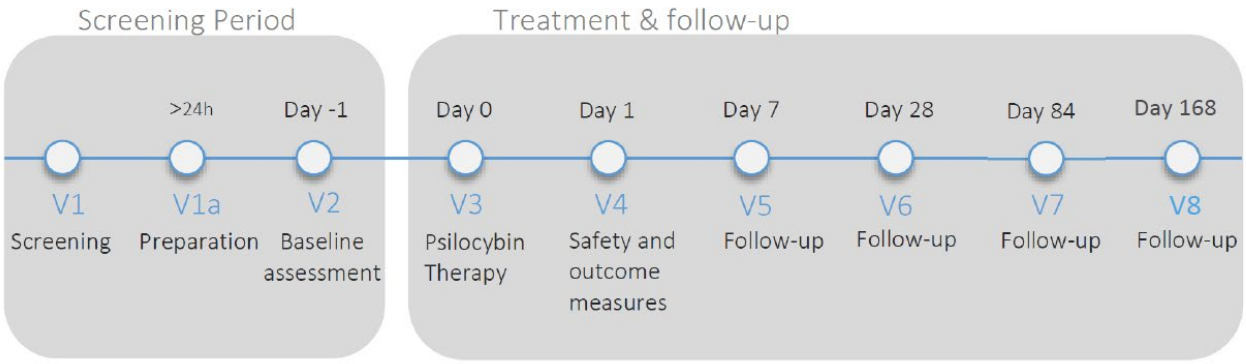
Study visit:

The research study involves a minimum of 7 in-person visits over a minimum of 6 weeks, followed by 2 optionally virtual visits separated by a period of 12 weeks. Additionally, participants will have the option to complete a virtual, semi-structured qualitative interview after the first of the final two optionally virtual follow-up visits. The screening period will last at least 1 week and the follow-up period after the psilocybin session will last 24 weeks. The approximate durations for each visit are: Screening visit 1- 4 hours, dosing preparation visit 2- 60-90 minutes each, baseline- 4-5 hours, Day 0- 9 hours, Day 1- 3 hours, Week 1- 3 hours, Week 4- 3-4 hours, Week 12- 3 hours, Week 24- 2 hours. Visits will be conducted at the Altman Clinical and Translation

Research Institute (ACTRI) or virtually via UCSD Health Zoom. All procedures listed below are considered experimental and will be billed to the research study.

If participants are taking antidepressants, antipsychotics or other serotonergic medications upon the screening visit (V1), they will be notified that they must discontinue these medications for at least two weeks or five elimination half-lives, whichever is longer, prior to enrolling in this study and remain off these medications through visit V5 (7 +/- 2 days after the dosing session V3). Participants will have the option to have their medication titration be overseen by either the study clinician, or their current psychiatrist. For participants who meet all other eligibility factors and who will undergo the two week washout period overseen by the study clinican, two additional in-person visits will be scheduled. During the in-person tapering visits, all participants will be supported by the study clinician. During these two additional visits, (between V1 and V1a), vitals and weight will be taken to ensure continued medical stability and the designated study nurse will be in frequent contact with the participants to monitor for withdrawal and worsening of symptoms. At these visits, the study clinician will conduct a mental status examination, assess for any change in symptoms, and assessed for suicidality with the C-SSRS at each contact/visit. For participants who meet all other eligibility criteria and who will undergo medication tapering overseen by their current psychiatrist, the study team will be in frequent contact with the participant's clinical care team, as well as the participant, to ensure that effective care and support throughout the tapering process, as well as to monitor for any rebound effects or worsening in depression/eating disorder symptoms.

Study Schematic



Study Design: This is a Phase II, single-centre, single-dose, open-label trial to explore safety, tolerability and acute (1 week) and sustained (24 week) effects of a 25mg dose of psilocybin on core symptoms of AN. The study population will include adult males and females, 18 to 40 years of age, with AN. Participants with AN are defined as those who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for AN.

Participants will be recruited primarily through referrals from the University of California San Diego (UCSD) Eating Disorders Center and the community including referrals from general practitioners and health services.

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview (MINI), the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD), Colombia-Suicide Severity Rating Scale (C-SSRS), via medical history, an ECG, a physical examination

(including weight and height for a BMI measurement), blood tests, a urinalysis, urine drug screen, and urine pregnancy test for women of childbearing potential, and vital signs. Demographic information will also be collected as well as details regarding the patients previous treatments for AN

Once a patient completes all screening assessments, the investigator(s) will review the results and issue approval, if the patient is eligible [V1].

All patients will have 2 preparatory sessions with the study therapists to discuss safety and effects of psilocybin, personal and medical history, and current symptoms. The preparatory sessions will occur on V1a and Baseline V2.

The day before the psilocybin session (≥ 24 hours (h) after Screening [V1]; V1a, Day -7; V2, Day -1), the participants will undergo a baseline assessment that will consist of the Spielberger State-Trait Anxiety Inventory (STAI;[19]), the Eating Disorder Examination (EDE), the Eating Disorder Examination - Questionnaire Short Form (EDE-QS;[20]), the Quick Inventory of Depressive Symptomatology (QIDS), the Clinical Impairment Assessment Questionnaire (CIA), the Readiness and Motivation Questionnaire (RMQ), the Eating Disorder Inventory (EDI), the Physical Appearance State and Trait Anxiety Scale - State and Trait Versions (PASTAS; [22]), the Columbia-Suicide Severity Rating Scale (C-SSRS), the Body Image State Scale (BISS; [23]), food related rituals and obsessions using the Yale-Brown-Cornell Eating Disorder Scale Self-Report Questionnaire (YBC-EDS-SRQ; [24]), Clinical Global Impressions of Severity and Improvement scales (CGI-S, CGI-I), visual analogue scales (VAS) to rate hunger, fullness and desire to eat, vital signs including weight (measured by a health professional), urinalysis, urine drug screen, urine pregnancy test (only for women of childbearing potential), ECG, and blood tests. After baseline data is collected, the team will complete a final review to ensure the participant's continued eligibility [V2]. Participants cannot be progressed to the psilocybin dosing session [V3] until eligibility is confirmed and approval is received.

Treatment intervention is conducted the day (+/-1 day) after the Baseline visit and comprises preparation, psilocybin dosing, and follow up (post-administration/integration) with the study therapist(s) for each subject [V3].

The participant will receive two preparation sessions (V1a and Baseline (Day -1 [V2]) by a specially trained study therapist. The sessions serve to continuously assess for participant readiness and continued eligibility via vitals and weight monitoring and clinical assessment by the therapist. The sessions will focus on discussion of possible psilocybin effects, preparing participants for the dosing session by practicing relevant therapeutic techniques to reduce avoidance and anxiety, including discussion and practice of mindfulness and relaxation techniques eliciting AN-relevant therapeutic goals, building rapport, and establishing therapeutic alliance. The preparation sessions will determine the therapist's assessment of participants' readiness as determined by understanding of procedures, mastery of skills reviewed and no change in symptoms that would be disqualifying based on exclusion criteria. The preparation sessions will be conducted only after the participants' eligibility is confirmed. The final preparation session will be conducted the day before the dosing session Baseline, Day -1).

The 25mg psilocybin administration session (Day 0 [V3]) will last approximately 8 h and will be supported by the lead therapist and an assisting therapist. Prior to the dosing, participants will complete the following: urine drug screen, vital signs, weight measurement, and health status and current medications will be reviewed. Throughout the dosing session, the participant's heart rate will be recoreded, using a continuous heart rate monitor. A full description of the activities of the psilocybin administration session can be found in Appendix 19.2 (this information was taken from a Therapist Manual, a protocol approved for the investigation of psilocybin plus psychotherapeutic support for treatment resistant depression (probably reference study number or IND). After the acute effects of the psilocybin pass, participants will complete a self-report questionnaire (5D-ASC) and then will be evaluated for safety by the study psychiatrist and accompanied home by a previously agreed upon support person.

On Day 1 [V4], the day following psilocybin administration, participants will be seen in person for the post-treatment/integration session. This session will include a safety check (C-SSRS, vital signs, weight measurement, ECG, blood tests, and a urinalysis), completion of all questionnaires completed at baseline, a qualitative post-dosing interview, and a discussion regarding the patient's experience during the psilocybin session. All participants will participate in two integration sessions. In addition to the above stated objectives of V4 sessions, sessions will focus on the therapist

assisting participants in attending to and processing therapeutic content relevant to their illness(es). Therapeutic techniques used for integration sessions are specified in the Appendix 19.2.

Participants will be followed up at 7 (+/-2) days (Day 7 [V5]) and again at 28 (+/-3) days (Day 28 [V6]). At Day 7 [V5] and Day 28 [V6], participants will complete the same measures as per the Baseline (V2) assessment including safety assessments: CSSR-S, weight measurement, blood test, vitals and an ECG. At the end of the Day 28 [V6] assessment, participants will be asked how they would feel about receiving subsequent doses of psilocybin to explore perceived acceptability of multiple dosings. At 84 (+/- 7) days (Day 84 [V7]), participants will again be followed up and will be weighed and complete all self-report questionnaires and clinical interviews as they completed at Baseline (Day -1, [V2]). Participants will also complete a questionnaire consisting of yes/no reflection questions, relating to how the Psilocybin dosing whether the experience was meaningful or impactful for their recovery. However, since the EDE measures eating disordered behaviours and thoughts over 28 days, it will therefore only be asked at Day 28 and Day 84, and not Day 7 or Day 1. At 168 (+/- 12) days (Day 168 [V8]) participants will be followed up for the final time. This visit will be an entirely self-report virtual visit. Participants will be sent the same set of questionnaires completed at prior visits, and will be asked to provide a weight measurement.

Participants will be seen at the clinic for Screening Period [V1, V1a], Baseline (Day -1, [V2]), Dosing Session - Day 0 ([V3], 25mg dosing), Day 1 [V4], Day 7 [V5], and Day 28 [V6]. Day 84 [V7] may be completed in clinic or virtually, depending on logistical feasibility and participant preference. If Day 84 is virtual, weight measurements will be sent be self-reported by the participant or shared by a member of the participant's primary care team. In the event that a participant or key study team member exhibits COVID symptoms, incuding cough, congestion, fever, and loss of taste, and is unable to receive COVID test results before a scheduled in-clinic visit, or in the event that the in-clinic visit becomes either logistically infeasible or burdensome, all therapist lead assessments (C-SSRS, CGI-S, CGI-I) and therapy sessions will be completed virtually via UCSD Health Zoom, which is HIPPA compliant. Adverse events, serious adverse events (SAEs) and concomitant medication and therapy will be recorded at all contacts with the participant.

Participants will have the option to participate in a semi-structured qualitative interview post-Day 84 [V7]. This interview will be audio recorded if the participant provides audio recording consent. Interview questions will focus on participants' experience within the study, and ask participants to reflect on any changes in motivation for recvoery, anxiety, body image, and eating habits. Participants who do not consent to the optional semi-structured qualitative interview and/or the audio recording will not be excluded from the study. The interview requires approximately 1-2 hours and will be completed virtually via UCSD Health Zoom, which is HIPPA compliant.

Premature Discontinuation: If the participant's participation in the study is terminated prematurely for any reason, the reason for such ET should be documented and the EOS procedures should be performed. A termination electronic Case Report Form (eCRF) page should be completed for every participant, whether the participant completes the study or not. The reason for any ET should be indicated on this form; as much information should be provided as possible. The primary reason for a participant discontinuing early should be selected from the following standard categories of ET:

- *Screen Failure:* Participant does not qualify to participate in the study.
- Lack of efficacy: *Participants who meet the following criteria after the psilocybin session will be evaluated by a study clinician, hospitalized if appropriate, and treated according to the national standard of care guidelines. They will be followed until the end of the study if informed consent is maintained:*
    - become suicidal as determined by clinical judgement and/or by C-SSRS as stated in the Exclusion Criteria
    - showed scores of QIDS increased by < 20% between the visits
    - showed scores of QIDS increased by < 20% for 3 consecutive visits
    - Medical instability as determined by abnormal and clinically significant results on the physical examination, vital signs, ECG, or laboratory tests at Screening (V1), such as liver function tests (LFTs) two times greater than the upper limit of normal, reduced glomerular filtration rate (GFR) and elevated creatinine two times of upper limit of normal.
    - Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic,

renal or any other major concurrent diagnosis.

- *Adverse Event*: Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the participant, are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to the IP.
- *Death:* The participant died.
- *Withdrawal of Consent*: The participant or caregiver desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the participant gave a reason for withdrawing, it should be recorded in the eCRF.
- *Protocol Violation*: The participant's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g, drug noncompliance, failure to return for defined number of visits). The violation necessitated early discontinued from the study.
- *Lost to Follow-Up*: The participant stopped coming for visits and study personnel were unable to contact the participant.
- *Noncompliance:* The participant was noncompliant with study visits or procedures.
- *Other*: The participant was discontinued for a reason other than those listed above, such termination of study by COMPASS

List and Description of Measures

Construct	Measure	Type
Efficacy Assessments		
Anxiety	Speilberger State-Trait Anxiety Inventory	Self-report questionnaire
Depression	Quick Inventory of Depressive Symptomatology (QIDS)	Self-report questionnaire
Eating Disorder Symptomatology	Eating Disorder Examination (EDE)	Semi-structured interview
Clinical Impairment Assessment	Eating disorder specific impairment	Self-report questionnaire
Eating Disorder Symptomatology	Eating Disorder Examination Questionnaire Short Form (EDE-QS)	Self-report questionnaire
Eating Disorders Readiness	Readiness and Motivation Questionnaire (RMQ)	Self-report questionnaire
Eating Disorder Behaviors and Risk	Eating Disorder Inventory -3 (EDI-3)	Self-report questionnaire
Food Related Obsessions and Rituals	Yale Brown Cornell Eating Disorder Scale Self-Report Questionnaire (YBC-EDS-SRQ)	Self-report questionnaire
Body Image	Physical Appearance State and Trait Anxiety Scale - State and Trait Versions (PASTAS)	Self-report questionnaire
Body Image	Body Image State Scale (BISS)	Self-report questionnaire
Novelty Seeking and Harm Avoidance	Temperament and Character Inventory (TCI)	Self-report questionnaire

Visual Analogue Rating Scales	hunger, fullness, desire to eat	Rating scale
Psychedelic intensity/experience	5D- Altered states of consciousness questionnaire	Self-report questionnaire
Symptom severity, treatment response, and efficacy of treatment	Clinical Global Impressions of Severity and Improvement (CGI-S, CGI-I)	Clinician rating scales
*Participant experience (1-day time point only)	Qualitative interview	Semi-structured interview
Pharmacokinetics	Serial blood samples	Lab draw
Safety Assessments		
Columbia Suicide Severity Rating Scale		Semi-Structured Interview
ECG		IN-house measurements by ACTRI professional
Vital signs (including weight kg)		IN-house measurements by ACTRI professional
Clinical Laboratory tests including liver function tests		IN-house measurements by ACTRI professional
Adverse Events		
Screening Assessments		
MINI Neuropsychiatric Interview		Interview
McLeann Screening Instrument for Borderline Personality Disorders		Self-report questionnaire
Vital signs (including weight kg)		IN-house measurements by ACTRI professional
Clinical laboratory tests including liver function tests		IN-house measurements by ACTRI professional

Measures Description:

Mini International Neuropsychiatric Interview
The MINI was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-5 and International Classification of Diseases-10. Validation and reliability studies have been done comparing the MINI to the Structured Clinical Interview for DMS-5 Patient Edition and the Composite International Diagnostic Interview (a structured interview developed by the World Health Organization). Version 7.0.2 of the MINI will be used for this study. The results of these studies show that the MINI has similar reliability and validity properties, but can be administered in a much shorter period (mean 18.7 ± 11.6 min, median 15 min) than the above referenced instruments. It can be used by clinicians after a brief training session

McLean Screening Instrument for Borderline Personality Disorder

The MSI-BPD is a commonly used measure to assess for BPD. The scale consists of 10 items based on the DSM-5 BPD criteria; the first 8 items represent the first eight criteria in the DSM-5 for BPD diagnosis, while the last two questions assess the paranoia and dissociation criteria for BPD. Scores for the MSI-BPD range from 0 to 10, with each item rated as "1" if present and "0" if absent. A score of 7 or higher indicates a likelihood for the participant to meet criteria for BPD, and is subject to confirmation either by evaluation with lead therapist, medical record review, or history of BPD diagnosis from a psychiatrist/PCP/therapistThe MSI-BPD will be collected at Screening (V1) only.

Spielberger State-Trait Anxiety Inventory (STAI): The STAI is a widely used instrument that consists of separate self-report scales for measuring "state" and "trait" anxiety. (10 minutes)

Quick Inventory of Depressive Symptomatology (QIDS-SR): The QIDS is a self-report, 16-item measure of depressive symptom severity derived from the 30-item Inventory of Depressive Symptomatology (IDS).

Eating Disorder Examination (EDE): The EDE is a standardized interview used to measure severity of the characteristic psychopathology of EDs. It provides a measure of the range and severity of eating disorder features. It can also generate operational eating disorder diagnoses.

Eating Disorder Examination Questionnaire (EDE-QS):
The *Eating Disorder Examination-Questionnaire Short Form* (EDE-QS) consists of 12 items that assess the core symptoms of eating disorders. The EDE-QS was developed as a 12-item version of the EDE-Q with a response scale ranging from 0 to 3 that captures essential symptoms of Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder. Scores of items are summed, ranging from 0 to 36 and higher scores indicate greater eating disorder symptoms. Eating disorder symptoms are reported for the preceding seven days.

Yale Brown Cornell Eating Disorder Scale Self-Report Questionnaire (YBC-EDS-SRQ): is a self-report questionnaire which characterizes and quantifies preoccupations and rituals associated with eating disorders.

Physical Appearance State and Trait Anxiety Scale: State and Trait Versions (PASTAS): The PASTAS is a 16-item measure that assesses anxiety about physical appearance.

Body Image State Scale (BISS): is a 6 item self-report scale that measures an individuals' affective/evaluative body image states. The BISS has good validity and is sensitive to momentary fluctuations of body-image evaluation, which allows for the assessment of body image states versus trait-level body image.

Visual Analogue Scales: are designed specifically for this study and will measure the degree of hunger/fullness and desire/lack of desire to eat. Participants will mark the degree of their experience in relation to the anchors along a 100mm continuum.

Clinical Impairment Assessment: is a 16 item self-report measure that measures psychosocial impairment of eating disorders.

Readiness and Motivation Questionnaire (RMQ): is a self-report questionnaire used to assess readiness for change across all eating disorder diagnoses and to establish its psychometric properties. The RMQ provides stage of change, ineranlity, and confidence scores for each of 4 eating disorder symptom domains (restriction, bingeing, and cognitive and compensatory behaviors).

Temperamental and Character Inventory (TCI): is a self-report questionnaire consisting of 240 items constructed to assess 7 basic dimensions of personality. Of the 240 items, 75 items will be used to assess 2 temperament dimensions (Harm Avoidance and Novelty Seeking) that have established associations with anxiety disorder and eating disorder diagnoses. The TCI assesses change in ED-associated temperament traits in the months following the Psilocybin dosing.

5D Altered Dimension States Questionnaire: The 5D-ASC measures the acute drug effects using five primary dimensions and respective subdimensions to assess alterations in mood, perception, and experience of self in relation to environment and thought disorder. The 5 dimensions include: *oceanic boundlessness*, *anxious ego dissolution*, *visionary restructuralization*, *auditory alterations*, and *reduction of vigilance.* This will be administered immediately after the

psilocybin session on Day 0 (V3).

Clinical Global Impressions of Severity and Improvement Scales: The CGI-S and CGI-I are rating scales which measure symptom severity, treatment response, and the efficacy of treatments in treatment studies. It is a 3-item observer-rated scale meant to assess a patient's functioning prior to and after initiating medication in trials. These scales will be completed by the study therapist to provide estimates of global baseline illness severity in the sample and a change in illness severity following treatment.

Columbia Suicide Severity Rating Scale: The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior over a specified time period. The measurement of suicidal ideation is based on 5 "yes" or "no" questions with accompanying descriptions arranged in order of increasing severity. If the patient answers "yes" to either questions 1 or 2, the intensity of ideation is assessed in 5 additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behavior is assessed by asking questions categorizing behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and nonsuicidal self-injurious behavior.

Qualitative Interviews: A semi-structured qualitative interview will be asked on Day 1 (V4) regarding the patient's views on their psilocybin experience and acceptability of treatment. This questionnaire was designed specifically for this study. A more detailed and optional semi-structured qualitative interview will be virtually administered post-Day 84 [V7] asking questions surrounding changes in eating disorder sympomology post-dosing, motivation for participation, features of the psychedelic experience, and constructive feedback.

Reflection Questions: A brief, 7 item questionnaire formulated by the study team based on exisiting psychedelic literature. The questionnaire consists of simple "yes" or "no" questions to quantitatively assess how meaningful and impactful the treatment was. Questions ask participants to reflect on their quality of life, valuation in their appearance, sense of identity, feelings of spirituality, anxiousness, and perspective on life endeavors after treatment.

Assessment Schedule

					Time Since Psilocybin Treatment				
	Screening[1]	**Dosing preparation**	**Baseline (Day -1)**	**Psilocybin Session (Day 0)**	**Day 1**	**Day 7**	**Day 28**	**Day 84**	**Day 168 (EOS/ET)**
Visit	**1**	**1a**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Location Visit	**Clinic**	**Clinic or Virtual**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic or Virtual**	**Virtual**
Allowable Window	**-**		**+ < 7 days**	**None**	**None**	**±2 days**	**±3 days**	**±7 days**	**±12 days**
Clinician Assessments and Procedures									
Informed Consent	✓								
Medical History	✓		✓						
Inclusion/exclusion Criteria	✓		✓	✓					
MINI 7.0.2	✓								
C-SSRS	✓	✓	✓	✓	✓	✓	✓	✓	
EDE			✓				✓	✓	

CGI-S, CGI-I			✓		✓	✓	✓	✓	
Qualitative assessment					✓				
Vital signs	✓		✓	✓✓	✓	✓	✓		
Physical examination	✓								
Weight measurement			✓	✓	✓	✓	✓	✓	✓
12-Lead ECG	✓		✓		✓	✓	✓		
Clinical laboratory tests[2]	✓		✓		✓	✓	✓		
Urinalysis[2]	✓		✓		✓				
Urine drug screen[2]	✓		✓	✓					
Urine pregnancy test[3]	✓		✓						
Documentation of contraceptive method to be used[4]	✓								
Preperation		✓	✓						
Psilocybin dose				✓					
Integration					✓	✓			
Prior/Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓	
AE/SAEs	✓	✓	✓	✓	✓	✓	✓	✓	
Participant Completed Assessments									
MSI-BPD	✓								
QIDS			✓		✓	✓	✓	✓	✓
STAI			✓		✓	✓	✓	✓	✓
EDE-QS			✓		✓	✓	✓	✓	✓
CIA			✓		✓	✓	✓	✓	✓
BISS			✓		✓	✓	✓	✓	✓
RMQ			✓		✓	✓	✓	✓	✓
PASTAS			✓		✓	✓	✓	✓	✓
EDI			✓		✓	✓	✓	✓	✓
YBC-EDS-SRQ			✓		✓	✓	✓	✓	✓
TCI			✓		✓	✓	✓	✓	✓
VAS measures			✓		✓	✓	✓	✓	✓
5D-ASC				✓[5]					✓
Reflection Questions								✓	

Laboratory Test

Vital Signs	• Orthostatic heart rate and blood pressure will be measured (supine, after at least 5 min of rest, then after standing 1 minute and 3 minutes). The difference between supine and standing blood pressure will inform eligiblity. Respiratory rate, body temperature, and pulse rate will be obtained at Screening, Baseline, Day 0, Day 1, Day 7, and Day 28 [V1, V2, V3, V4, V5, and V6 respectively]. Vitals will be obtained twice on Day 0 [V3].
Clinical Laboratory Tests	• Heaematology haemoglobing, haematocrit, red blood cell count, mean corpuscular haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin concentrate, white blood cell count (with differential), and platelet count • Chemistry: albumin, alkaline phosphate, alanine aminotransferase (ALT), amylase, asparate aminotranserase (AST) bicarbonate, bilirubing (direct, indirect, and toatl), Calcium chloride, creatine kinase, C-reactive protein, creatinine, gamma-glutamyltransferase, glucose, lactate dehydrogenase, lipase, magnesium phospate, potasium, proteint-total, sodium urea (blood urea nitrogen), and uric acid
Urine Samples	• Urinalysis: a urinalysis will be performed for blood, glucose, ketone, proteing, pH, specific gravity, nitrite, leukocytes, bilirubin, urobilinogen at V1, V2, and V4 • Urine Drug Screen: for illicit drugs or drugs of abuse at Screening [V1], Baseline [V2], and Day 0 [V3]. Results of a positive drug screen will be reviewed by the study clinican for pattern of use. • Urine pregancy test: a dipstick test in women of childbearing potential at Screening [V1] and Baseline [V2].

Investigational Product:

5-capsule oral psilocybin dose of 25 mg.

Primary Endpoint:

The primary endpoint is the the safety, tolerability and feasibility of psilocybin in adult patients measured by:

- Incidence and occurrence of AEs from Baseline (Day -1 [V2]) to Day 84 [V7], and from Day 1 [V4] to Day 84 [V7].
- Incidence of clinically important changes in ECG parameters from Baseline [V2] to Day 1 [V4], Day 7 [V5] and Day

28 [V6].

- Clinically relevant variations and clinically important patterns in heart rate, QTc Interval, and breathing rate throughout the dosing period using a continuous heart rate monitor device.
- Incidence of clinically important changes in laboratory tests from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5] and Day 28 [V6].
- Incidence of clinically significant changes in vital signs from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5] and Day 28 [V6].

Secondary Endpoint:

The secondary endpoints are to assess the effect of 25mg psilocybin on:

- Change in EDE total scores from Baseline (Day -1 [V2]) to Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in weight (kg) from Baseline (Day -1 [V2]) to Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in trait anxiety total score on the STAI from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in state anxiety total score on the STAI from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in PASTAS trait total score from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in PASTAS state score from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in BISS total score from Baseline (Day -1 [V2]) to Day 168 [V8].
- Change in YBC-EDS-SRQ total score from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8]..
- Change in EDI total score from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7] and Day 168 [V8]..
- Change in EDE-QS total scores from Baseline (Day-1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8]..
- Change in TCI novelty seeking and harm avoidance subscale scores from Baseline (Day-1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].

Exploratory Endpoint:

- The primary endpoints assessed as incidence at Day 1 [V4] and Day 28 [V6].
- The secondary endpoints assessed as change from Baseline to Day 1 [V4] and Day 7 [V5] (with the exception of the EDE and EDE-QS)
- Change in weight (kg) from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in QIDS total scores from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in CIA total scoes from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in VAS measures from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], and Day 84 [V7].

- Change in Readiness and Motivation Questionnaire (RMQ) scores from Baseline (Day -1 [V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Change in Clinical Global Impressions of Severity and Improvement (CGI-S, CGI-I) scores from Baseline (Day -1[V2]) to Day 1 [V4], Day 7 [V5], Day 28 [V6], Day 84 [V7], and Day 168 [V8].
- Summary of the 5D-ASC on the day of the psilocybin dosing [V3].

Links between psychedelic intensity and experience (via the 5D-ASC) and eating disorder outcomes will also be explored and patient experience and acceptability of the treatment summarised at V3, V4, V6, V7, and V8.

Efficacy Endpoint:

- EDE
- EDE-QS
- STAI
- QIDS
- RMQ
- YBC-EDS-SRQ
- PASTAS
- BISS
- CIA
- EDI
- VAS measures for hunger, fullness, desire to eat
- 5D-ASC
- CGI-S
- CGI-I
- TCI

Safety Assessments:

- ECG
- Vital signs including weight (kg)
- Clinical laboratory tests including liver function tests
- AEs and Serious AEs
- C-SSRS

Statistical Procedures:

Analysis Sets

The Safety Population will consist of all enrolled participants who receive study treatment. This population will be used for all summaries of participant accountability, demographic and baseline data, and safety information, including AE incidence.

The Full Analysis Set (FAS) will consist of all participants who receive the dose of investigational product and will be

used for all summaries of efficacy.

The Per Protocol (PP) Population will consist of all participants in the FAS who do not have a major protocol deviation defined as a deviation which may significantly affect efficacy for that participant. Major protocol deviations will be reviewed and determined prior to database lock.

Efficacy Analyses

The FAS and the PP populations will both be used for each primary and secondary endpoint, if the two sets are not identical. For each of the primary, secondary and exploratory endpoints, measuring change from Baseline, summary statistics will be provided. We will use descriptive statistics (e.g., mean, standard deviation, frequencies) to summarize all variables (e.g., number of missed doses or drop-outs, AEs) at all time-points. We will evaluate change in all constructs assessed, and weight across baseline, and study days using t-tests ($\alpha = .05$, two-sided). Due to the small sample size for this initial pilot study, we will also examine effect size.

Additionally, the 5D-ASC score will be summarised on the day(s) of the psilocybin session(s).

Safety Analyses

Safety data will be presented for the Safety Population. Safety will be evaluated based on AEs, ECGs, clinical laboratory tests, and vital signs including weight.

Safety Assessments

Columbia-Suicide Severity Rating Scale

The C-SSRS will be used to assess suicide potential or tendency as a study entry criteria and monitored throughout the study.

The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior over a specified time period. The measurement of suicidal ideation is based on 5 “yes” or “no” questions with accompanying descriptions arranged in order of increasing severity. If the patient answers “yes” to either questions 1 or 2, the intensity of ideation is assessed in 5 additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behavior is assessed by asking questions categorizing behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and nonsuicidal self-injurious behavior.

If any item(s) on the C-SSRS are answered “yes”, the primary investigator or physician investigator must review the patient’s responses in order to (a) at screening and Baseline determine the patient’s study eligibility and potential need for referral to a mental health professional, and (b) during the study evaluate the patient’s need for appropriate medical management such as a referral to a mental health professional.

A significant risk of suicide is defined as a “yes” in answer to (a) questions 4 or 5 on the suicidal ideation section; or (b) any questions on any item in the suicidal behavior section. This must be reported as an AE or SAE as appropriate and followed up accordingly. Additionally, if a patient responds “yes” to any of the suicidal ideation questions 1 through 3, the investigator should apply clinical judgment to determine the need for reporting this as an AE or SAE and the need for any appropriate referral. The C-SSRS will be collected at Screening, Dosing Preparation, Baseline, Day 0, Day 1, Day 7, Day 28, and Day 84 (V1, V1a, V2, V3,V4, V5, V6, and V7 respectively).

Vital Signs

Orthostatic heart rate and blood pressure will be measured supine, after at least 5 min at rest, and then while standing up after 1 minute and 3 minutes. The difference between supine and standing blood pressure will inform eligiblity. Respiratory rate, body temperature, and pulse rate will be obtained at Screening, Baseline, Day 0, Day 1, Day 7, and Day 28 [V1, V2, V3,V4, V5, and V6 respectively]. During the dosing session [V3], participants will have 2 sets of vitals taken: one prior to dosing and one post-dosing.

During the dosing session, the participant will wear a continuous heart rate monitor, collecting heart rate, breathing rate, and QTc interval data.

Electrocardiogram

Standard 12-lead ECGs will be obtained at Screening (V1), Baseline (V2), Day 1 (V4), Day 7 (V5), and Day 28 (V6).

Clinical Laboratory Tests

Blood samples will be obtained at Screening (V1), Baseline (V2), Day 1 (V4), Day 7 (V5), and Day 28 (V6) for the following:

- *Haematology:* haemoglobin, haematocrit, red blood cell count, mean corpuscular haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin concentration, white blood cell count (with differential), and platelet count.

- *Chemistry:* albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (direct, indirect, and total), calcium, chloride, creatine kinase, C-reactive protein, creatinine, gamma-glutamyltransferase, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, protein-total, sodium, urea (blood urea nitrogen), and uric acid.

Urine samples will be obtained at Screening (V1), Baseline (V2), Dosing (V3), and Day 1 (V4) for the following:

- *Urinalysis:* A urinalysis will be performed for blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, and urobilinogen at V1, V2, and V4.

- *Urine Drug Screen:* for illicit drugs or drugs of abuse at Screening (V1), Baseline (V2), and Dosing (V3). Results of a positive drug screen will be reviewed by the study clinician for pattern of use.

- *Urine Pregnancy Test*: a dipstick test in women of childbearing potential at Screening (V1) and Baseline (V2).

Laboratory samples will be analysed by a local laboratory (CALM) to ensure consistent interpretation of results. In the event of an unexplained clinically significant abnormal laboratory test value, the test should be repeated and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Adverse Events: All AEs occurring after the participant signs the ICF and up to the last study event will be recorded. Any AEs occurring before the start of treatment (i.e., before the dose of the IP on Day 0 [V3]) will be recorded in the medical history. Any AE ongoing at (EOS/ET) will be followed until resolution or no longer considered clinically significant by the investigator.

Psychotherapy:

The psychotherapeutic goals of the psilocybin session are to:

- Ensure psychological safety essential for optimal clinical efficacy
- Allow participant 's subjective experience to unfold naturally within the boundaries of the therapeutic intention set at the preparation
- Maintain participant 's attention and awareness on the experience of the present moment thus allowing exposure and processing of the challenging emotional states and memories
- Generation of insights and solutions for the resolution of challenging personal situations, conflicts and traumatic experiences

Psychotherapeutic methods of the psilocybin session have the following objectives:

- Psychological safety: effective management of anxiety is essential to safety, tolerability and efficacy of psilocybin. It has also been shown in previous studies that severe prolonged anxiety in the beginning of the experience could adversely affect the efficacy of psilocybin, therefore the management of anxiety during the onset of the session is an essential skill of psilocybin therapists. Anxiety during the onset of action is not uncommon, and the therapists are specially trained to recognize and actively manage participants through such periods of anxiety until the subject is comfortable enough to continue on their own. Therapists are asked to validate the feeling of anxiety without providing interpretations of perceptual disturbances or guiding participants towards a particular image or memory, other than encouraging them to stay relaxed and open to the emergent experiences. In the modern research setting, any anxiety during the onset of psilocybin action responded well to reassurance and meditation.
- Self-directed Enquiry and Experiential Processing: In preparation for the psilocybin session, therapists demonstrate and practice skills of self-directed inquiry and experiential processing with participants. Participants are encouraged to face and explore their experience, including the challenging ones. During the peak and later stages of the session, self-directed inquiry and experiential processing become essential for participants to develop a different perspective on their personal challenges and conflicts, and to generate their own solutions. Such self-generated insights are not only therapeutic because of the emotional resolution, but also empowering to participants. This approach is used in MDMA-assisted psychotherapy for treatment of PTSD and is particularly helpful in the event of emergent traumatic memories.

Structure of the Psilocybin Session

The psilocybin session is supported by two trained therapists with a higher degree in a counseling/therapy profession of an M.A and/or a PHD. The study psychiatrist will be in the immediate vicinity of the session to respond to any emergencies.

On the day of the session, participants come in early in the morning with the goal to take the dose around 7:30 am. Nursing staff will take vital signs, weigh the participant, and take a urine sample for a drug screening. A standardized 300-500 calorie breakfast will also be provided upon arrival, consisting of easily digestible selections that were selected by the participant beforehand. Health status and current medications will also be reviewed while the participant completes his or her pre-dosing breakfast. Prior to dose administration, a team of psychotherapists will review the rules and structure of the session with the participant again. Once all the questions are answered and the participant reconfirms their consent for the session, the participant will be fitted to a continuous heart rate monitor, and will be administered the dose (5 capsules) with a full glass of water. Delaying the intake of dose may induce unnecessary anxiety in participants, therefore it is recommended to have the treatment room prepared for the start of the session before participant's arrival. The treatment rooms in all trial sites are furnished in soft furniture in muted colours to create a non-clinical calming feel. All treatment rooms are equipped with a high-resolution sound system that allows for simultaneous ambient and earphone listening. The playlist is designed jointly with experts from Johns Hopkins University and the Imperial College London to provide nonverbal guidance.

Participants will then be encouraged to lie down, practice relaxation and breathing exercises, and listen to calming music. Therapists might want to revisit the intention for the treatment session with the participant and again, ask the question *"What would it look and feel like to be free of an eating disorder?"* Such revisions immediately prior to the session provide an implicit direction for the subjective experience during the psilocybin session. Once the effects of psilocybin become noticeable, participants are encouraged to put on Mindfold eyeshades and earphones and focus on their internal experience. Psychotherapists will sit on both sides of the patient's couch. Psychotherapists are discouraged from reading, using laptops or phones, eating or drinking other than water during the first 2-3 hours of the session.

If adequately prepared, participants should tolerate the onset well using the skills practiced during preparation period. Psychotherapists offer support in the form of reminders, encouragement, grounding hand holding, or active guiding, should the challenging experiences arise. The best ways for support, and boundaries of physical touch are discussed and practiced during the preparation. In general, therapists are instructed to provide therapeutic grounding above shoulder level only. In case of participants with a history of physical and sexual abuse, therapeutic touch should be limited to hand and forearm areas only, or to the form of physical support that was agreed to during preparation.

Therapists are also trained in the skill of recognizing when to allow the participant's experience to unfold naturally. During the peak experience, especially in the case of non-dual or full ego-dissolution experience, participants are usually silent and may appear comfortable, even blissful. In such cases, no active guiding is needed.

As the drug effects start to subside, participants again might become engaged with emergent narratives.

In case of prolonged anxiety or distress, therapists may choose to actively guide participants through such experiences without interpreting or judging the experiences or giving advice. Once participants are comfortable, they are encouraged again to engage in introspection.

At the end of the session and after the effects of the psilocybin are no longer evident, participants become more talkative and interactive. The role of the therapists now is to ensure that experiential processing is complete with some emotional resolution. In those cases, where there is still anxiety or despair at the end of the session, participants are encouraged to relax and reflect for a longer period of time. The provisions are made for therapists to stay with the participant until the effects of the drug have fully subsided, and participant is assessed to be comfortable and fully sober. This is assessed through engaging in 'small talk' about non-contentious topics unrelated to the content of the session. Participants and therapists are discouraged to discuss the content of the session until the next day to avoid premature consolidation of the insights. At the end of the session, therapists and participants might have a light meal together to mark the closure of the session. Participant's family or friends might also be invited to join the meal if participant consents. After the safety assessments, participants will be discharged in the care of a family member or a friend. Please refer to the section of safety for more detailed information on discharge assessments and unexpected adverse events.

Before the Session:
On the day of the psilocybin session, the participant arrives at the clinical center between 7AM and 7:30AM. It is essential for the therapist and the supportive assistant (the therapeutic team) to prepare the room and take care of all the logistics prior to the participant's arrival. The therapist and assistant should welcome the participant shortly following his/her arrival and allow for the expression of any questions or concerns. Since participants are likely to be at least mildly anxious, it is important to validate their anxiety and assure them it is common to be anxious prior to a new experience. The time following arrival and prior to entering the treatment room should be as minimal as possible, as "waiting outside" (even if reading a book) tends to increase anxiety.

The behavioral rules are reviewed again. The participant should reconfirm that he/she:

- Will stay in the room for the duration of the session.
- Will follow the therapist's instructions as all directions are given entirely to ensure their safety.
- Have an accurate mutual understanding of ways the therapist can provide support during the session, including interpersonal grounding, guided imagery and breathing exercises.

Key components of mental set/intention are also reviewed:

- Every experience is welcome; nothing to censor or avoid.
- Face anything that looks potentially frightening as rapidly and openly as possible.
- Reach out for grounding, support or sharing at any time.
- Remember key instructions: Trust, Let Go, Be Open.
- Remember to breathe deeply if needed.
- You'll never be left alone.
- No need to entertain the therapist/assistant.
- This is your day. We're with you, whether you need us or not.

Once all the agreements are reconfirmed and the participant is settled in the treatment room, the therapeutic team offers 5 capsules of the IP with a full glass of water. After the participant takes the capsules and drinks all the water, he/she should settle back on the couch, listen to the music, focus on his/her breathing and relax. This is often when the participant may share photographs or meaningful objects he/she has brought, or when he/she may leaf through an art book—often with the therapist and assistant sitting on both sides of the participant on the couch. As the initial effects of psilocybin are beginning

or about to begin, a final trip to the bathroom is offered before the participant reclines and accepts the eyeshade and headphones. Before the drug's effects begin, it is helpful to re-establish the participant's stated goals for the treatment and to revisit the question: "What does feeling better or recovery feel like?" The participant is reminded that their primary task during this session is to simply collect new and interesting experiences which can then be discussed with the therapist during the integration phase. The therapist can remind the participant of the purpose of the psilocybin therapy and the role of experiential processing, namely allowing the participant to be open and curious to whatever arises and encountering thoughts and feelings previously unknown to them. It should be emphasized that this process inherently requires letting go and a willing passivity to the psychedelic experience; the willingness to let go is correlated with better outcomes in psilocybin therapy.[4] The therapist should remind the participant that the therapeutic team will be supporting them at all times.

Participants are encouraged to relax and focus on internal experience, but are allowed to move around, sit up, talk, and stretch as needed. Occasionally participants may feel the need to move around or express their emotions physically. All expressions, including physical expressions are encouraged.

Setting and Music: A standardized playlist is employed in all sessions regardless of the apparent level of psilocybin dosage. It begins with soft background music before the participant enters the room and continues through the various phases of a typical high-dose session. It may include some periods of silence. In intense sessions, the choice of music rarely appears to influence experiential content, but it can provide strong nonverbal support and engagement with unfolding inner content unique to each participant. In the latter two hours of a psilocybin session, most any music can be appreciated and explored. The participant is instructed to accept and explore the music as the day progresses, irrespective of their usual personal preferences or current emotional responses. Criticizing and trying to control the music has often been found to be a symptom of resistance to unfolding content. Therapists may choose to deviate from the playlist in highly unusual situations but allowing the standardized playlist to unfold generally proves effective and frees the therapist to focus on the participant. The playlist is skillfully designed to provide variety in a context of accumulated experience with many different persons undergoing psychedelic therapy.

Managing Anxiety: Transient anxiety is often reported as participant's encounter changing psychological content. Such anxiety might be viewed as natural and even necessary. It can manifest in different ways, ranging from mild intractability and avoidance of the emerging experiences to extreme paranoia. In most cases, anxiety resolves on its own accord and can be minimized with skillful interpersonal support. Psilocybin provides a unique opportunity for a participant to normalize anxiety and view it as excitement and experience the encounter with honest ambivalence. During the acute onset of action, the participant might experience perceptual changes in visual, auditory or olfactory modes, and a range of unusual physical sensations. These experiences could be anxiety-provoking, particularly in psychedelically naïve participants. During preparation, the therapist encourages the participant to become curious about these experiences and to freely explore them. If the participant continues to manifest anxiety and emotional distress, the therapist may offer therapeutic touch or interpersonal grounding, if that is something the participant has agreed to during preparation and has been rehearsed. The therapist encourages the participant to focus inwards and fully immerse him/herself in all aspects of the experience. The participant may want to practice guided imagery or breathing relaxation techniques in preparation.

Managing Distractions and Avoidance: Occasionally, the participant will try to avoid emerging experiences or distract him/herself while trying to regain cognitive control over the unusual state of their mind. The therapist must recognize that such distractions could take different forms. The participant might want to engage in a conversation or prematurely describe in detail their experience, visions or insights. When this occurs, the therapist and assistant aim to remain as silent as possible, thereby enabling the participant and his/her inner experience to direct the course of the psilocybin session. Active listening skills may be required if the participant engages the therapist in conversation; this should be paired with prompts to encourage the participant to continue focusing attention on present experiences. Here the therapist does not add any new information or even words, but still acknowledges the participant.

Challenging Shifts versus Adverse Events: Emotions and feelings can shift quickly during psilocybin experiences. Such shifts must be differentiated from distress that requires active guidance. It is essential that the therapist use his/her clinical judgment to establish whether the participant is in need of the therapist's quiet and non-intrusive presence, or active guidance. During preparation, the participant has been informed that they can ask for support from the therapist for any

reason at any time, especially when they do not feel able to navigate through a particular experiential sequence. Therapists may talk with clinicians/therapists and may coordinate psychotherapy outside the trial. Information should be provided regarding the integration of the psilocybin session with any psychotherapy the participant is currently receiving (and will continue to receive throughout the duration of the study and cannot have been initiated within 21 days of baseline).

Emergency Protocol: The general principle is that if the participant cannot be calmed down through all the available methods, and is presenting a current threat to him/herself or others, the first choice of medical treatment is either oral or IV benzodiazepines. The participant should be made safe in the least invasive and distressing way possible. Note, however, that in research with psilocybin in different university settings over almost two decades, there has never been a need for rescue medications. PRN emergency rescue medications will be administered by the PI and/or attending psychiatrist with the support from the study clinician, who will be using behavioral anxiety management strategies to attempt to reduce participant distress. Rescue medications will be given orally. If the patient cannot be calmed down through all of these methods, which would be highly unlikely and is deemed a threat to self or others, the 911 emergency response team will be called to provide assistance and further assessment.

Peak Experience: With adequate dosage and an acute onset of action, a 'peak' experience may occur about 60-90 minutes after ingestion. Factors that influence the quality and intensity of peak experiences include the participant's ability to stay with whatever arises in awareness, their ability to relax and let go of expectations and fears, dose of psilocybin, etc. Non-dual experiences have been shown to positively correlate with the magnitude and durability of the clinical response, so this state needs to be attended with care. The goal of the therapist is to encourage and support the participant in being fully present and relaxed in this state. Verbal communication should be minimal. Participants who reach peak experience tend to be quiet; even non-responsive. In the unlikely event that a participant would express a need to prematurely attempt to share such an experience, it should be viewed as distraction or avoidance. The therapist needs to encourage the participant to stay quiet and focus on the sensations, insights and feelings, and to collect as many details about the experience as possible so as to be able to relate the story later. However, in true ego-loss and non-dual experiences, there is no ego present. When recalled in memory, participants usually claim such states to be beyond language. Transcendent non-dual experiences are frequent, especially during high-dose psilocybin sessions. There may be perceptions that extend well beyond the usual sense of self, such as feelings of oneness in which the participant experiences an openness and enhanced connection to their own humanity and to the surrounding environment. Such experiences can be difficult to interpret and may challenge a therapist's own worldview. The therapist is not required to understand, support or even have an opinion about the nature or content of these experiences, but it is essential that they validate them and convey openness toward the participant's own view of them without dismissing or pathologizing any experience based on its unusual content. These experiences may provide the participant with a perspective that goes beyond identification with their personal narrative. It is equally important that a therapist not show disappointment when a participant does not report a profound transcendental experience. The therapist should remain mindful of his/her own reactions and responses to the participant's experiences and validate any and all of them. However, that doesn't mean that the therapist must agree with unusual, magical thinking. Validation of the experiences simply means acknowledging the courage of opening up to the experience and the possibility that any experience will serve the intention of the session.

Conclusion of the Psilocybin Session*:* The drug effects last for 4-6 hours. During the final phase, it's important that the participant doesn't prematurely terminate the session by excessive talking. Even if little appears to be happening, periodic returns to the couch with music, headphones and eyeshade often provide for not only unexpected new experiential content, but safe and complete closure. The use of music is continued and light conversations between the therapist and participant are encouraged. This serves the dual role of re-orienting the participant to everyday reality and enabling the therapist to assess for immediate risks. By having a light casual conversation about dinner or the weather, the therapist assesses whether the participant is struggling to re-enter reality, or is distressed by the content of the session. This can be discussed over a light meal with the participant, which—if they choose—can include the participant's family members. The therapist needs to be mindful that the participant is adequately reoriented to everyday reality, and be certain that the participant is fully competent to travel before making the journey home. If the participant requires a longer period of time to return to normality, the therapist is expected to remain with the participant. If the participant requires emotional support due to a difficult session, the therapist is required to support the participant until the discomfort is resolved and the participant is fully back in everyday reality. The therapist should use open questions and empathic attention, as in

previous sessions, to ensure that the participant feels supported.

Specific Criteria for Discharge from the Facility on the Day of Drug Administration: Participants will remain in the treatment facility for a full 8 hours after the start of the session, to ensure that the psilocybin effects have fully subsided. Participants are then assessed for safety by the therapists and the study clinician. A second set of vitals will be taken before discharge, and the continuous heart rate monitor will be removed. Participants are observed in the facility to ensure that they are fully ambulatory, have good balance, are psychologically stable, and can perform activities of daily living. Participants are also asked to complete the C-SSRS (Columbia-Suicide Severity Rating Scale) and 5D-ASC (5 Dimensions of Altered States of Consciousness). These scales will be performed by the study team and will allow the clinician to assess participant's emotional and cognitive stability, risk for suicidality and whether the perception- altering effects of psilocybin have subsided. When judged safe and functional, participants are discharged in the care of a friend or a family member who will stay with the participant overnight. Plans for the follow-up visit the next morning are confirmed prior to discharge. When the participant is ready to leave, he/she will be given information regarding the time and location of the next session (safety assessment and integration within 24 hours of the psilocybin session) as well as contact numbers if help is needed before then. The therapist is expected to be available 9am-5pm on weekdays and the emergency services number can be used on weekends and evenings. The participant must agree not to drive or use alcohol during the evening following the psilocybin session. The therapist should check in with the participant and family member(s) later in the evening to confirm that the participant is comfortable and safe.

Planning for Unexpected Adverse Events: Participants who may have an unusually prolonged experience or remain in severe distress and are considered at risk for adverse reactions will be asked to stay for observation overnight and will be supported by another study team member. In case of psychotic reaction, participants will be assessed by a study psychiatrist and hospitalized as needed. The emergency protocol specifies oral benzodiazepines, followed by antipsychotics as needed. In over 2,000 research sessions with psilocybin, there has never been a need for emergency interventions.

Accountability: The investigator must keep an accurate accounting of the number of IP units delivered to the site, administered to participants, and returned to its designee (COMPASS LIFE SCIENCES IS PROVIDING THE IP) or other disposition (i.e., destroyed on site at request of COMPASS or its designee) during and at the completion of the study. The IP must be administered to participants only by an appropriately qualified person. The IP is to be used in accordance with the protocol by participants who are under the direct supervision of the investigator. Investigators should maintain records that document adequately that the participants were administered the IP dose specified by the protocol and reconcile all IPs received at the site before final disposition. At the end of the study, or as directed, all IP, including unused, partially used, and empty containers, will be returned to the sponsor or its designee.

Concomitant Therapy: All prescription and non-prescription medications (e.g., over-the-counter drugs and herbal supplements) that participants report taking during the 30 days prior to Screening (V1) will be assessed and recorded at that visit. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use. Concomitant medication refers to all drugs and therapies used from the time the ICF was signed through the end of study participation. Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit. All as-needed (pro re nata, PRN) prescriptions should be converted to reflect actual number of pills or dose taken per day.

Permissible Medications: Medications for the management of concurrent anxiety and insomnia, or nonpsychiatric medications that have a potential psychotropic effect are permitted within the following limitations. From the initial Screening Visit (V1) through final study visit (V7, EOS), participants are permitted adjunctive use of benzodiazepines (up to 2 mg of lorazepam equivalents per day for insomnia and anxiety if it is not taken within 12 h before the psilocybin dose. Prescription and nonprescription medications with psychoactive properties that are used as needed for non-psychiatric conditions (e.g., pseudoephedrine for allergies or cold symptoms) should be used no more than 2 times a week and not in the 12 h before any study assessment. Documentation of the use of adjunctive anxiolytics, hypnotics, or medication with potential psychotropic properties (including over-the-counter preparations) will be obtained at each clinic visit. Therapy considered necessary for the participant's welfare may be given at the discretion of the study clinician. If

the permissibility of a specific medication/treatment is in question, please contact COMPASS or its designee.

Women of child bearing potential:
A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile (i.e., has had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy). A woman who is not of childbearing potential is considered to be postmenopausal after at least 12 months without menstruation. The following methods of contraception, if used properly and used for the duration of the study, are generally considered highly effective:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Periodic abstinence (i.e., calendar, symptothermal, or post ovulation methods, and tubal ligation/occlusion) are not an acceptable form of contraception for this study. These methods of contraception also apply to partners of male participants. The investigator and each participant will determine the appropriate method of contraception for the participant during the participation in the study. This will be documented at Screening (V1). If a participant or the partner of a male participant becomes pregnant during the study, the investigator will notify COMPASS or Worldwide immediately after the pregnancy is confirmed. The PI will not provide no cost birth control, but a urine pregnancy screen will be conducted at the following visits: screening (V1), baseline (V2) and on the day of the dosing (V3) before medication is administered. Medical staff will verbally review contraception methods with participants who are women of child-bearing potential at the timepoints V1 and V2.

Prohibited Medications: Participants are to be discontinued from serotonergic medications at least 2 weeks or five elimination half-lives, whichever is longer, prior to Baseline. Participants will meet with the therapist and study psychiatrist during this time (for 2 preparatory sessions to ensure continued eligibility for the study and to assess for changes in symptoms due to medication withdrawal). Serotonergic medications include but are not limited to the selective-serotonin reuptake inhibitors, selective-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, antipsychotics, and/or lithium. Common medications in these classes are noted below but the list is not exhaustive; the medical monitor should be contacted if there is any question that a used medication is thought to be in one of these classes but is not listed below. These medications are not to be reintroduced to the participant until after Day 28 (V6, Week 4). Participants who require concomitant medication(s) specifically for the treatment of depression at any time through the duration of the study will be assessed for reasons of resuming their medications and followed until 12 weeks post psilocybin administration. The study clinician should initiate treatment of symptoms of depression per local site practice and may change the venue of therapy (i.e., outpatient to inpatient) if deemed clinically necessary. The intervention may be a combination of somatic (e.g., approved antidepressant medication) and no somatic (various forms psychotherapy, e.g., CBT) whose therapeutic intention is remediation of the depressive episode. Because the anticipated half-life of psilocybin is approximately 3 h, and only 1 administration of test product is permitted, no known issues regarding PK or pharmacodynamic interactions are envisioned within approximately 7 days of product administration.

Rescue Medication: Rescue medications may be used during and after the psilocybin session. The decision to medicate a participant will depend on whether the monitors and responsible physician judge that they are capable of maintaining the safety of the patient and others without medical intervention.

- Benzodiazepine anxiolytics is the pharmacological intervention of choice in case of acute psychological

distress or disinhibition (e.g., medications such as lorazepam or alprazolam that have a rapid onset, a short time until peak plasma concentration, and a short duration of therapeutic action; the oral route is preferable because IV injection procedures may further exacerbate the participant's anxiety).

- Antipsychotic medications (e.g., risperidone) should be available in the event that an adverse reaction escalates to unmanageable psychosis.

In case of development of acute anxiety or psychotic symptoms requiring pharmacological intervention, the participant will stay in a clinic until the full resolution of the symptoms (overnight if required). The participant may be discharged from the clinic when, in the opinion of investigator, the condition has stabilized. The participant is to return home accompanied by a family member, friend, or chaperone. The site is to be notified by the participant that they have returned home safely, and in the absence of receiving a phone call site staff will directly contact the participant. Information of how to manage subjects during difficult psychological states are detailed in the Study Manual.

Compliance: *Administration of IP will be supervised by study personnel to ensure compliance.*

10. HUMAN SUBJECTS

Eligibility Criteria:

Inclusion Criteria

1. 18 to 40 years of age at Screening (V1).
2. Current or past diagnosis of anorexia nervosa. A current diagnosis will be based on medical records, clinical assessment, weight, and documented completion of the version 7.0.2 MINI (informed by Diagnostic and Statistical Manual of Mental Disorders-5, the standard classification of mental disorders used by mental health professionals). A past diagnosis, also informed by the DSM-5, will be based on medical records, past documentation of a diagnosis, a clinical assessment, and documented completion of the version 7.0.2 MINI.
3. Agree for the study team to maintain contact with their primary care team for the duration of the study.
4. Ability to complete all protocol required assessment tools without any assistance or alteration to the copyrighted assessments, and to comply with all study visits.
5. Participant capacity to consent (assessed via investigator judgment).

Exclusion Criteria

Medical Exclusion Criteria:

These criteria will be determined during the Screening Period (V1 and V1a) and Baseline (V2). Exclusion assessments that will be rechecked on the day of dosing are marked with an Asterix.

6. BMI < 16 kg/m^2 *
7. Medical instability as indicated by significant (>3kg) weight loss, orthostatic heart rate (>20 BPM increase in heart rate) and blood pressure (>20 mmHg decrease in systolic or >10 mmHg decrease in diastolic). *

   i. Participants deemed as medically unstable may be waitlisted in the case that the investigator evaluates the abnormal result as mild or transient in nature. Waitlisted participants must be re-assessed and cleared at the discretion of the investigator at a later date in order to re-enroll in the study and proceed to subsequent visits.
8. Women who are pregnant, nursing, or planning a pregnancy in the near future. Male and female participants who are sexually active must agree to use a highly effective contraceptive method throughout their participation in the study. Women of child bearing potential must have a negative urine pregnancy test at Screening (V1) and Baseline (V2), and the psilocybin dosing session day *
9. Cardiovascular conditions: active anticoagulant therapy, recent stroke (<1 year from signing of ICF), recent myocardial infarction (<1 year from signing of ICF), uncontrolled hypertension (blood pressure >140/90 mmHg), or clinically significant arrhythmia within 1 year of signing the ICF.
10. Uncontrolled or insulin-dependent diabetes.

11. Seizure disorder.
12. Use of psychedelics, including psilocybin, within one year prior to Screening [V1] assessment
13. Positive urine drug screen for illicit drugs or drugs of abuse at Screening (V1) and Baseline (V2) and the psilocybin dosing day. Any positive urine drug test will be reviewed with participants to determine the pattern of use and eligibility will be determined at the investigator's discretion *
14. Current enrollment in any investigational drug or device study or participation in such within 30 days prior to Screening (V1)
15. Abnormal and clinically significant results on the physical examination, vital signs (e.g., body temperature <96F, 35.6C), ECG, or laboratory tests at Screening (V1) and Baseline (V2), such as liver function tests (LFTs) two times greater than the upper limit of normal, reduced glomerular filtration rate (GFR), elevated creatinin two times of upper limit of normal, or electrolyte disturbances (hypokalemia, hyponatremia, hypophosphatemia).

    i. Participants deemed as medically unstable may be waitlisted in the case that the investigator evaluates the abnormal result as mild or transient in nature. Waitlisted participants must be re-assessed and cleared at the discretion of the investigator at a later date in order to re-enroll in the study and proceed to subsequent visits.
16. Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal or any other major concurrent illness that, in the opinion of the investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if he/she takes part in the study
17. Non-english speakers

Psychiatric Exclusion Criteria:

18. Current or past history of schizophrenia, psychotic disorder, bipolar disorder, significant history of mania, delusional disorder, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder as assessed by medical history and a structured clinical interview
19. McLean Screening Instrument for Borderline Personality Disorder >7 at Screening (V1) and clinical confirmation of diagnosis either through evaluation with the lead therapist, medical records review, or affirmation of Borderline Personality Disorder diagnosis from the participant's psychiatrist, PCP, or therapist.
20. Currently taking a serotinergic medication. All serotinergic medication must be discontinued at least two weeks or five elimination half-lives, whichever is longer, prior to baseline.
21. Current (within the last year) alcohol or substance use disorder as informed by DSM-5 at Screening (V1).
22. Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the Colombia-Suicide Severity Rating Scale (C-SSRS) within the past year, at Screening or at Baseline, or; (2) suicidal behaviors within the past year, or; (3) clinical assessment of significant suicidal risk during subject interview (pre-treatment V2 sessions).

22. Other personal circumstances and behaviour judged to be incompatible with establishment of rapport or safe exposure to psilocybin, including exposure to psilocybin within the past year and use of psychedelics, such as ayahuasca, during the current episode.

11. RECRUITMENT AND PROCEDURES PREPARATORY RESEARCH

We plan to recruit 20 participant with AN over a 1 year time period (we anticipate recruitment to begin in February 2021). Patients will be recruited from the UCSD Eating Disorders Center and from the community. UCSD Eating Disorders Center staff and community therapists will be notified of the study and encouraged to notify patients of a study evaluating the safety, tolerability and initial efficacy of psilocybin for anorexia. Flyers (attached for approval) will be posted in the UCSD ED center and distributed to community providers which include a study contact for participants to call and initiate contact to review the details of the study, and assess for eligibility using the screening assessments.

In order to recruit participants who are potentially eligible for the current study (e.g. adults with AN), a waiver of consent and partial wavier of HIPPA authorization is requested. Specifically, this will allow for an identification of adult female patients at the UCSD EDCTR who are seeking treatment for AN meet these primary inclusion criteria for the research.

This would be of minimal risk to potential participants, as the information would be accessible only to members of the study staff directly involved with recruitment. Additionally, as there are several ongoing studies at the ED center at any given time, participants who are approached to determine their potential interest in the study (see below) would not be unduly singled out. Further, the waivers would not adversely affect the rights and welfare of the participants, as their decision whether or not to participate in the study if approached would have no effect on the care that they are receiving at the Center. Importantly, the study recruiter will emphasize to the patients that participation in the research in no way influences eligibility to receive treatment at UCSD or elsewhere, and that participation is entirely voluntary. Participation of patients will be scheduled to reduce interference with treatment programming, and during recruitment. It will also be emphasized that participants may withdraw their consent and decide not to participate at any time with no impact on their treatment at UCSD or elsewhere.

A research recruiter will obtain access to the UCSD ED program census to identify adult women with AN as their primary ED diagnosis. The research recruiter will obtain permission from the patient's individual therapist at the Center prior to making contact with the patient to describe the research opportunity. As noted above, the study recruiter will emphasize that participation is entirely voluntary and will have no influence on their treatment or any other care that they receive at UCSD. Both this initial contact and any subsequent participation will be scheduled to minimize any interference with treatment activities

Once contact is initiated by potential participants, the study contact (trained research coordinator) will have a thorough discussion of the study, (including adequate time for the potential subject to have all issues clarified) and briefly review the procedures. If the subject agrees and meets initial eligibility, then the screening assessment will be Scheduled to assess for eligibility.

We will employ recruitment strategies that have been shown to be effective, including: a) contacting participants who have been in our previous studies and who appear to be appropriate potential participants for this current study, provided they have given written permission for recontact; b) posting flyers in local businesses and at several local university campuses; c) we will also use social network websites such as Facebook to advertise and provide information about our study. Specifically, we will provide information about the ongoing study on social network websites, including results of published studies and preliminary results that have been presented at public meetings. We will also provide a link back to our website where more information regarding our study and related studies is available. We will not allow participants to become "friends" on our social network site. This will prevent the disclosure of name and other identifying information to other visitors of the site

12. INFORMED CONSENT

Full informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements. The investigators or a trained research coordinator will fully explain to the subject the purpose of the study and all of its procedures, as well as its potential risks prior to entering into the study. Each patient will receive a copy of the consent, HIPPA authorization and the patient's bill of rights. A copy of the consent form(s) has been electronically attached to this application.

At any point prior to the Psilocybin dosing session (V3), participants will also be asked to sign a consent to contact a support person form. This optional form grants permission to the investigator, as well as trained personnel delegated by the investigator, to contact the participant's elected support person at any point throughout the participant's enrollment in the study. The form also requests the support person's contact information, including phone number, email, home address, and address for the night post-dosing. Additionally, the form asks that participants acknowledge that the consent person's role within the study, which include transporting the participant to and from their Psilocybin dosing session and Day 1 Visit, as well as staying with the participant the night prior and night following the dosing visit. By signing the form, the participant agrees that the support person has been made aware of the form and agreed their role, as well as to be contacted. Electing not to sign the consent to contact a support person form will not impact a subject's eligibility.
HIPPA authorization will be a stand-alone document requiring a signature from each subject who agrees to participate in the study. State and federal privacy laws protect the use and release of health information. Under these laws, the University of California or the health care provider cannot release health information to the research unless the subject gives their permission. The research team includes the researchers and people hired by the University or the sponsor to do the research. The subject will be required to give permission under separate HIPAA authorization. If the subject decides to give their

permission and to participate in the study, they must sign this form as well as the informed consent form. This form describes the different ways that the researcher, research team and research sponsor may use the health information for the research study. The research team will use and protect the information as described in the informed consent form. The study subjects will be furnished with copies of the signed informed consent form, the optional consent to contact a support person form, the HIPAA consent, and the Experimental Subject's Bill of Rights.
Should participants elect to participate in the virtual semi-structured interview post-Day 84 [V7], and consent to being audio recorded, the participant will be provided a stand-alone audio recording consent form. This form grants the study team permission to use audio recordings from the semi-structured qualitative interview for research and training purposes.

13. ALTERNATIVES TO PARTICIPATION

The alternative to participation is not to participate.

14. POTENTIAL RISKS

Side effects associated with psilocybin: Over 1000 psilocybin sessions have conducted in modern scientific studies in patients and healthy volunteers. Hundreds of patients were treated with psilocybin in the 1950s and 60s and millions of people have taken psilocybin in the form of magic mushrooms in recreational settings.

The most common acute side-effects associated with psilocybin are anxiety and nausea. In addition, psilocybin can raise blood pressure and heart rate but not to dangerous levels.

It is not uncommon to feel anxious after being given the drug but with proper support and guidance, these effects are short-lived. We know that developing a relationship of trust in the therapist and feeling safe and relaxed in their surroundings can minimize the feeling of being anxious in psilocybin sessions. Subjects will receive psilocybin in a calm environment, have eye-shades and listen to relaxing music playing quietly for most of the drug experience. They will be fully supported by a psychiatrist and psychologist/therapist and other members of the research team, who will be specially trained and competent in dealing with any problems that might arise.

So-called 'flashbacks' or a sense of re-experiencing psychedelic drug effects when no drug has been taken, have been described in scientific literature but have not been reported in modern research studies with psilocybin.

It is possible that the subjects' anorexia may fail to respond to the study medication they receive in this trial and even deteriorate further. The study team will be in frequent contact with the subjects throughout the study to record their eating disorder symptoms.

Below is a summary of the frequency of effects with psilocybin:
Common (over 50%):
-Visual and other sensory distortions, feeling of unreality & changed sense of time
-Anxiety at the onset of the drug effects
-Increased heart rate and blood pressure
-Suppression of appetite

Less common (about 10-40%):
-Nausea
-Dizziness, blurred vision, drowsiness & sleepiness
-Headache
-Temporary suspiciousness

Rare (< 10%):
- "Flashbacks" or hallucinogen-induced persistent perceptual disorder (HIPPD). This adverse effect is seen rarely following recreational use and has not been reported in scientific studies done under supportive clinical conditions
-Worsening of mental state after the drug experience (very rare and was not seen in similar studies).

ECG: The pads may irritate the skin and cause itching and redness.

Potential Reproductive Risks: Women should not breastfeed a baby while on this study. It is important that subjects use

birth control while on this study. To ensure that participants are not pregnant, a urine screen will be conducted prior to drug administration.

Risks of stopping medication prior to study participation: The major risks of stopping psychotropic medications are mostly associated with stopping medication abruptly. We would not require participants to stop medication abruptly. If you meet all other eligibility criteria, participants can undergo the two-week washout period, and two additional in-person visits will be scheduled. Stopping medications slowly over a two-week period is generally safe. Risks may include symptoms similar to withdraw or worsening of symptoms. During the tapering period, participants will be supported by the study clinician. During the two additional visits, (between V1 and V1a), vitals and weight will be taken to ensure continued medical stability and the designated study nurse will be in frequent contact with the participant to monitor for withdrawal and worsening of symptoms. At these visits, the study clinician will conduct a mental status examination, assess for any change in symptoms, and assessed for suicidality with the SSTS at each contact/visit.

Risks of blood draw: There is a possibility of mild discomfort, and rarely, a small arm bruise, clot, or infection may occur at the site of the blood draw. There is a rare risk associated with the chance of infection or lightheadedness or fainting due to blood withdrawal. The fear and anxiety in anticipation of the possibility of physical discomfort could lead to emotional discomfort. Care will be taken to avoid these complications.

Risks of rescue medication: The first choice of medical treatment for emergency rescue medications is either PRN oral or IV benzodiazepines. Short-term use of these medications is generally safe and effective. Benzodiazpines can cause acute effects such as drowsiness, increased reaction time, ataxia, motor incoordination, and anterograde amnesia. You will not leave the clinic until these side-affects have resolved. While the risks posed by mixing benzodiazepines with substances such as alcohol are considerable, they can have a positive impact on the impact of some mental health and neurological disorders when used correctly. Benzodiazepine overdose is rarely fatal unless the drugs are mixed with barbiturates, opioids, alcohol, or tricyclic antidepressants. The most common symptoms of benzodiazepine overdose are central nervous system depression and intoxication with impaired balance and movement control. Slurred speech will also be a sign.

Risk of drug testing: Psilocybin is undetectable in the blood by the morning following dosing. Hence there is no risk to employment/ future employment due to drug testing because of participating in this study.

Potential risk to fetal development: Reproductive toxicology studies have not been performed to establish risk to the fetus; however, the results of Ames test, the human lymphocyte micronucleus assay and the *in vivo* rat micronucleus study clearly indicate no potential for genotoxicity with psilocybin. It is recommended to prevent or eliminate such risk, if any, women should not be pregnant or nursing and should be using an effective method of birth control when using psilocybin. We require that all participants agree to either abstain from sexual intercourse or use a reliable, effective contraception for this period, such as hormonal contraceptive, intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge or use of condom by the partner. Once a participant is enrolled in this study, pregnancy testing will be performed. If a participant has a positive pregnancy test, they may withdrawn from the study. If a participant may become pregnant or if there is any chance of pregnancy (e.g., late menstrual period), they will be infomred to contact the study personnel immediately so that the proper medical assistance and counseling can be provided.

Potential Loss of Confidentiality: All means will be employed to ensure that there is not a loss of confidentiality. Although study material will be kept private and inside a locked cabinet there is a slight possibility that a breach of confidentiality may occur. A special code de-identifying the research subject from the data and specimens collected will be assigned to all research subjects and their study material. Only the P.I., co-P.I. s and their research team will be able to link the research subject to the assigned code. It still may be possible, but highly unlikely, that the information in the research records could become known outside of the research setting.

Risk of Suicidality: If any of the study staff are concerned about participant safety based on C-SSRS scores or clinical judgment, an in-person assessment will be conducted to determine the need for any appropriate mental health referral or

hospitalization. If an imminent need of hospitalization would arise for any patient participating in the study, the site commits to expediently provide inpatient care. The participant will be escorted from the site, to the UCSD Jacobs Medical Center, which is across the street from the study site, to be assessed further for a psychiatric safety hold and inpatient stay. The Jacobs Medical Center is equipped to provide all facilities and services to give optimal healthcare to their patients. Current laws and regulations will be followed. The University of California, San Diego (UCSD) has their own acute inpatient section and own acute outreach team. The team connected to the study consists of a study nurse/coordinator, 2 psychiatrists and 2 psychologists. If needed patients can be sent immediately to the general hospital at any time. The emergency services, including the crisis resolution team and inpatient section at UCSD would be used. Any patient in the study can expect the highest level of support at any time.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. Subjects will be informed of any significant new findings.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Patients will be assigned code numbers to minimize risks to loss of confidentiality. All samples will be labeled with a study code number. The name, address, social security number, date of birth and all other personal identifiers will not be available on the sample and forms and we will not give out any information that identifies the patient to the researchers who use these samples and data. All publications and presentations will identify the subject by number only.

Phlebotomy will be performed by a trained phlebotomist experienced in blood drawing technique.

The study team, especially the therapist is specially trained and experienced to support participants during psilocybin treatment. If subjects were to have a challenging experience or negative reaction to psilocybin during or after the session, the research team will be able to help. These challenging experiences are usually temporary and resolve with reassurance and guided relaxation techniques. The chances are that there won't be a need to use any medication at all and the symptoms will be short-lived and resolve of their own accord. Subjects will be given a 'contact card' containing the contact details of all of the key members of the study team. In the unlikely event of a negative reaction to a study medication, subjects can contact the research team 24 hours a day.

If subjects' mental health was to deteriorate significantly during any point of the study and the therapist has serious concerns about the subjects' safety, then they would be obliged to involve local mental health services to determine how best to manage their condition.

Because Psilocybin commonly suppresses appetite in the hours post-dosing, a supervised breakfast will be provided in-clinic prior to the dosing. The pre-dosing breakfast is intended to ensure that participants have eaten prior to the dosing and to counteract the possibility of a caloric deficit during the Psilocybin dosing visit [V3].

The following plan should be followed to manage the occurrence of physiological adverse events during the psilocybin session:

- Headaches - Tylenol 650 mg taken by mouth, once.
- Symptomatic elevated BP - short-acting beta-blocker on the formulary once by mouth or IV.
- Chest pain - ECG, sublingual nitroglycerin, acetylsalicylic acid PO once and further evaluation as needed.
- Nausea, Vomiting – aspiration, precautions: ice chips.

Risk management of any suicide ideation will also be implemented. A significant risk of suicide is defined as a "yes" answer on the C-SSRS to (a) questions 4 or 5 on the suicidal ideation section; or (b) any questions on any item in the suicidal behavior section. If a patient responds "yes" to any of the suicidal ideation questions 1 through 3, the investigator should apply clinical judgment to determine the need for any appropriate referral.

During psychological screens and assessments, participants may report severe depression or suicidal ideation. We will immediately provide all participants, regardless of their responses, with a list of counseling and community mental health

resources at the conclusion of any study screenings.

If study staff identify participants whose responses indicate serious psychological conditions, including suicidal ideation, assessors will immediately review treatment referrals and crisis hotlines with the participant, encourage her to seek treatment, call 911, or go to the nearest emergency room, as appropriate. This may be upsetting to participants, and this risk is described ahead of time to participants in both the verbal consent script before phone screening and in the written consent form. All study staff are trained to ensure that the feedback is provided in a clinically sensitive manner.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Absolute confidentially cannot be promised because information needs to be shared as described below. However, information will be collected and shared following standards of confidentiality. Subjects' identity as a participant in this study will remain strictly confidential. Subjects will be identified in the study under a study-specific code. Should results of this study be published, subjects will not be identified through their name or personal information. All research records will be stored in a locked cabinet at all times. Computers used to store electronic data information, are password-protected and only accessible by the research team.

The study data will be stored in locked file cabinets, within a locked room. Only the Principal Investigators and designated members of the study team will have access to PHI. Inadvertent disclosure of PHI will be avoided by limiting access to study records and by placing only numerical codes instead of names or any other personally identifiable information on data forms. The code key linking subject names to ID codes will be locked separately from study records.

17. POTENTIAL BENEFITS

There may be no direct benefit to subjects from this study. However, the information gained from this study will help doctors learn more about Psilocybin in patients with Anorexia Nervosa.

18. RISK/BENEFIT RATIO

The risks of this study as listed above are minimal based on the safety profile and research that has already been conducted with psilocybin in psychiatric populations, however, the benefit to risk ratio may be large and is in favor of performing the study.

19. EXPENSE TO PARTICIPANT

There will be no cost to the subjects for this research study. Participants will be reimbursed for travel expenses for attending in-person study visits. In such cases, participants must provide study staff with receipts, bills, or invoices to document the travel reimbursement through UCSD. Participants will be reimbursed at UCSD's medical rate of 20 cents/mile for airfare and train expenses, or the actual cost of gas if the participant drives himself or herself. If the participant uses a rideshare app to travel to or from an in-person visit, he or she will be reimbursed for the actual cost of the ride, provided a screenshot of the receipt and the map that outlines the route of the rideshare.

20. COMPENSATION FOR PARTICIPATION

There is no compensation for this study (beyond the free treatment provided).

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator: Walter Kaye, MD, is director and founder of the University of California, San Diego Eating Disorder Treatment and Research Center and a Distinguished Professor of Psychiatry at UCSD. He has completed training relevant to clinical research including HIPAA certification, and Ethics training. Copies of licenses and certification are maintained.

Co-Investigator: Stephanie Knatz Peck, PHD is a clinical psychologist and the Director of the Intensive Family Treatment Program at the University of California, San Diego Eating Disorder Treatment and Research Center. She has completed training in the FDA- approved protocol for administering therapy and psychotherapeutic support alongside psilocybin administration and is a study therapist on the UCSD trial evaluating psilocybin in Treatment Resistant Depression (TRD).

Co-Investigator: Sidney Zisook, MD, is director of the University of California, San Diego Residency Training Program,

and a Distinguished Professor of Psychiatry at UCSD. He has completed training relevant to clinical research including HIPAA certification, and Ethics training. Copies of licenses and certification are maintained at the CTRI.

Stephanie Knatz Peck, PHD, Julie Trim, PHD, Diane Sterling, PsyD and Sabina Sehgal, PsyD: are the clinical therapists for the study. They have completed training relevant to clinical research including HIPAA certification, and Ethics training. Copies of licenses and certification are maintained at the CTRI.

Samantha Shao, Audrey Nunez, and Angeline Krueger are the study coordinators for this study and have completed training relevant to clinical research including Human Subjects certification, HIPAA certification, and ethics training. Alexandra Babakanian is a research assistant for this study and has completed training relevant to clinical research including Human Subjects certification, HIPAA certification, and ethics training. Kevin Yang, Daniel Sheinbein, and David Powell are fourth year medical student volunteers who will be assisting with data analysis, medical record review, and laboratory results review. All volunteers have completed all required training as listed above.

Archana Bhatt will serve as the regulatory contact for this study. She has completed training relevant to clinical research including Human Subjects certification, HIPAA certification, and ethics training.

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23. FUNDING SUPPORT FOR THIS STUDY

This study is being funded by Compass Pathways Limited.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT
N/A
25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER
Not applicable.
26. IMPACT ON STAFF
The impact on the research staff is minimal.
27. CONFLICT OF INTEREST
There is no conflict of interest with the sponsor or funder.
28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES
Not applicable.
29. OTHER APPROVALS/REGULATED MATERIALS
This study has received FDA-approval of the protocol and funding (negotiated by the Altman Clinical Research Institute on behalf of Dr Walter Kaye by the Office of Contracts and Grants Administration).
30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT
No Surrogate Consent will be pursued for this study.