Microdosing Psychedelics to Improve Mood: A Randomized Clinical Trial

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1.0 List of Abbreviations

AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CBD	Cannabidiol
CRF	Case Report Form
DMF	Drug Master File
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
DCC	Data Coordinating Center
EDC	Electronic Data Capture
GAD-7	General Anxiety Disorder-7 item scale
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IOS	Inclusion of Others in the Self Scale
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
LTFU	Long-term follow up
MDD	Major Depressive Disorder
NaSSA	Noradrenaline-Serotonin Specific Antidepressants
PHI	Personal Health Information
PHIPA	Personal Health Information Protection Act
PO	By Mouth
PRN	As Needed
QIDS	Quick Inventory of Depressive Symptomatology
RCT	Randomized Control Trial
RIMA	Reversible Inhibitors of Monoamine Oxidase
RR	Respiratory Rate
SCID	Structured Clinical Interview for DSM-5
SED	Serious Adverse Event
SOP	Standard Operating Procedures
SNRI	Selective Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors

TIA Transient Ischemic Attack

2.0 Introduction

This protocol is for a randomized, placebo-controlled crossover phase 1 study of the safety and efficacy of low doses of psilocybin in healthy subjects with depressive symptoms who meet DSM-5 criteria for diagnosis of a mild to moderate Major Depressive Disorder (MDD) and who are either unwilling to pursue standard treatment (psychotherapy and/or pharmacotherapy) or have previously been non-responsive to standard treatment. **This feasibility study will assess whether microdosing has a short-term impact on participant ratings of depressive symptoms.** Participants will be administered one dose of either placebo or psilocybin once weekly for four weeks, and then all participants will be administered a dose of psilocybin once weekly for four additional weeks. Short surveys will be collected once weekly three days after the administration of psilocybin/placebo, and follow-ups will occur for up to two years following the beginning of the trial. Using this design will maximize the experimental power to detect an effect if one exists and would inform future research on microdosing in terms of duration, effect size, and expectancy bias.

2.1 Rationale

Mental illness is a growing global problem: substance abuse and anxiety are currently the 5th leading cause of disability-adjusted life years lost in North America (Murray et al., 2012). Full-dose use of psychedelics has been linked to cessation of long-term substance dependence (Krebs & Johansen, 2012) as well as reduced anxiety and depression (Tupper, Wood, Yensen, & Johnson, 2015). The effects of high-dose psychedelics are thought to be mediated by hallucinations including altered perception and mystical experiences, awe towards nature, and a feeling that life is meaningful. This altered perception of reality, however, seriously impedes normal functions such as driving, working at an office, or caregiving. Microdosing psychedelics — ingesting doses below the threshold needed for hallucinations — does not occasion mystical experiences, yet users still report mental health benefits. Recent work suggests that despite the lack of altered perception, microdosing is indeed associated with improved mood and enhanced well-being, and that psilocybin, the active ingredient in “magic” mushrooms, is often consumed in microdoses (Anderson, Petranker, Rosenbaum, et al., 2019). This study will identify whether microdosing provides benefits similar to full-dose psychedelic use, will address the question of whether radically altered perception is needed for such benefits, and will pave the way for safer therapeutic applications. Establishing scientifically-informed guidelines for the safe and effective use of psychedelics is an important opportunity given the rise of unsupervised psychedelic use in the general population.

Major depressive disorder (MDD), also known as clinical depression, is a prevalent and debilitating psychiatric condition characterized by persistent and pervasive low mood, loss of

interest or pleasure in daily activities, and a range of cognitive and somatic symptoms. The impact of MDD extends beyond the realm of individual suffering, exerting a substantial burden on the affected individuals, their families, and society as a whole (Gutiérrez-Rojas et al., 2020). Addressing MDD is of paramount importance due to its significant negative consequences, including impaired social and occupational functioning, increased risk of comorbid psychiatric and physical disorders, elevated mortality rates, and heightened economic costs (Greenberg, 2018). By identifying novel treatments for MDD, stakeholders can foster timely and effective intervention, thus mitigating the adverse effects and promoting improved well-being and quality of life for those affected. Furthermore, addressing MDD can contribute to the reduction of healthcare utilization, enhance productivity, and facilitate the overall advancement of public health initiatives.

People suffering from MDD are a suitable population for microdosing trials due to the potential therapeutic effects of microdosing on symptoms of depression. Much of the existing literature on the utility of psychedelics focuses on the impact they have on Major Depressive Disorder (MDD), especially in treatment-resistant populations (see Goldberg et al., 2020 for a meta-analysis). A recent double blind study (Carhart-Harris et al., 2021) study showed therapeutic potential of psilocybin for the treatment of major depressive disorder. Recent research suggests that microdosing may offer a promising alternative therapy for MDD, as it has been associated with improvements in mood, motivation, creativity, and cognitive flexibility (Petranker et al., 2020), without inducing hallucinations or impairments in daily functioning. Furthermore, microdosing may help to mitigate some of the adverse effects associated with conventional antidepressant medication, such as tolerance, withdrawal, and side effects. Given the high prevalence of MDD and the limitations of current treatments, exploring the potential benefits and risks of microdosing in this population may provide valuable insights into novel therapeutic approaches for depression.

The dosing regime suggested will answer the question of interest while keeping participation in the study accessible to a broad community sample. Research suggests that the most common frequency of microdosing is every three days, with once weekly being the second most common frequency (Anderson et al., 2019). This study will use the latter pattern, administering a microdose once weekly such that individuals who have responsibilities such as work or childcare can come to the lab once a week, on the weekend. This dosing schedule allows measuring acute effects while participants are under the influence of the substance and the cumulative effects of microdosing over a period of 4 or 8 weeks.

Using sub-hallucinogenic amounts of psilocybin should cause no serious adverse events, as doses 10 times larger or more have been administered to hundreds of participants (see Goldberg et al. 2020 for a meta-analysis). A recent study also found that among almost 7,000 microdosers no serious adverse effects were reported, with restlessness, fatigue, and confusion being the most commonly reported side effects (Petranker et al., 2020). There is also some evidence to suggest that prolonged microdosing is safe: **A 6-week microdosing study showed**

no adverse results and some improvement in mood (Polito & Stevenson, 2019). Prochazkova et al. have also performed three studies on microdosing with no serious adverse events reported (see review by Prochazkova et al., in press**).** Additionally, online fora such as Reddit suggest that many more thousands of individuals have been using small amounts of psilocybin weekly or more frequently for months at a time.

In order to simulate the natural mushrooms used by millions of people around the world, this study will use a natural mushroom extract: PEX010. PEX010 is a standardized natural psilocybin extract of Psilocybe cubensis dry mushroom powder manufactured in a GMP environment. The naturally-occurring psilocybin present in PEX010 has the same chemical composition of synthetic psilocybin, which was originally isolated from Psilocybe mushrooms. Additionally, the concentrations of non-psilocybin constituents in these mushrooms are either quite low, inactive, or are completely removed during processing (See Investigator's Brochure). The only other psychoactive substance in PEX010 is trace amounts (>.01mg) of psilocin which is a metabolite of psilocybin and is accounted for and within tolerance of our experimental design. Since the only active ingredient in PEX010 is psilocybin, the rest of the application refers to the substance to be administered to participants as "psilocybin".

2.2 Background

Psilocybin 3-[2-(dimethylamino) ethyl]-1H-indol-4-yl] dihydrogen phosphate is a naturally occurring prodrug. The phosphate group is cleaved enzymatically in the body to produce psilocin, an agonist at a variety of serotonin receptors. This produces psychoactive and behavioral effects (Carhart-Harris et al., 2014; Nichols, 2004).

Animal Models:

There have been various non-clinical and clinical studies conducted that may have important implications for the trial in question. One study found that mice intraperitoneally injected with psilocybin exhibited faster extinction of the fear response than mice in the control condition (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013). The researchers found that mice in the low-dose condition (similar to the low-dose used in this trial) did significantly better at the response test than those in the high-dose condition. This meant that mice in the low-dose condition were faster at acquiring the link between the conditioned stimulus, an auditory cue, and the resultant shock that came after; they were also faster to pick up on the association between the conditioned stimulus and the absence of the shock than mice in the high-dose condition or the control group. This is relevant for our trial because the ability to relearn previously internalized behaviours is a key factor in overcoming various obstacles faced by individuals suffering from conditions such as depression and anxiety.

Another study that aimed to measure changes in neurotransmitters in mice brains concluded that administration of psilocybin increased levels of serotonin and dopamine, particularly in the

mesoaccumbens and mesocortical pathway (Sakashita et al., 2015). This is important for our study because the nucleus accumbens has been previously shown to be relevant to depression both in rodents and humans (Zangen, Nakash, Overstreet, & Yadid, 2001). Specifically, the dysregulation of the mesoaccumbens pathway due to decreased concentrations of various neurotransmitters including dopamine and serotonin has been linked to anhedonia in clinically depressed individuals (Shirayama & Chaki, 2006). Psilocybin could therefore be a potential means to increase levels of dopamine and serotonin and could be key in providing an anti-depressive and therapeutic effect.

An in vitro study of rat hippocampi found that administration of psilocybin caused a reduction in neuronal activity in hippocampal CA1 pyramidal neurons, associated with decreased glutamate transmission in the hippocampus (Moldavan et al., 2001). This is interesting from a therapeutic perspective because increased levels of glutamate in the brain are associated with symptoms of anxiety, depression, restlessness, and fatigue amongst other effects. While administration of psilocybin seems to primarily affect the serotonin receptors in the brain, it is important to note that psilocybin also affects other pathways that may contribute to changes in animal behaviour. A microdialysis study in awake rats found that systemically administered psilocin significantly increased extracellular dopamine levels in the nucleus accumbens with normal levels of serotonin. Conversely, they also observed significantly increased levels of serotonin and decreased levels of dopamine in the medial prefrontal cortex (Sakashita et al., 2015). A variety of mood disorders can be linked to an imbalance of neurotransmitters, specifically a lack of serotonin and dopamine. Psilocybin's ability to increase levels of dopamine and serotonin in the brain may be instrumental in reverting this change and allowing patients a way out of a downward spiral of mental health.

2.2.1 Known Risks

A substantial portion of participants treated with high dose psilocybin treatment also report difficult psychological experiences, including confusion, loss of sense of self, and transient feelings of anxiety (Griffiths et al., 2016). These experiences have been reported exclusively for high-dose studies of psilocybin (Barrett, Bradstreet, Leoutsakos, Johnson, & Griffiths, 2016).

There are almost no studies of adverse events or risks associated with low doses of psilocybin. Indeed, some studies have administered the amount we intend to use in this study as a placebo condition, with no adverse effects reported (Griffiths et al., 2016).

The information we have around low dose psychedelic risk comes from self-report data from users illicitly microdosing.

Surveys have suggested that the most commonly reported risk associated with microdosing psilocybin is that it is illegal, which can cause anxiety, but would not be a problem in an approved study.

However, several other side-effects have been documented by a sizeable proportion of participants. These include temperature dysregulation, numbing/tingling, insomnia, gastrointestinal distress, and reduced appetite between 18% (Anderson, Petranker, Rosenbaum, et al., 2019) and 5% (Hutten, Mason, Dolder, & Kuypers, 2019). Recent reviews of the literature indicate that psilocybin is not associated with harm or damage to any organ or system in the body (Nichols, 2004, 2016).

2.2.2 Known Benefits

One of the most commonly reported benefits from large doses of psilocybin has been a decrease in depression scores. Large doses of psilocybin have been shown to treat end-of-life depression (Griffiths et al., 2016) as well as treatment-resistant depression (Carhart-Harris et al., 2016). Large doses of psilocybin may also benefit anxiety (Grob et al., 2011), alcohol dependence (Bogenschutz et al., 2015), and obsessive compulsive behaviour (Moreno, Wiegand, Taitano, & Delgado, 2006).

Microdoses of psilocybin have yet to be studied in an active-control RCT. Recent survey work suggests that microdoses of psilocybin may enhance mood, focus, creativity, and social functioning (Anderson, Petranker, Christopher, et al., 2019; Anderson, Petranker, Rosenbaum, et al., 2019; Hutten et al., 2019; Prochazkova et al., 2018).

2.2.3 Justification of Dose

The safety and tolerability of psilocybin at a dose of up to 30mg per 70kg have been investigated in phase 1 and phase 2, single- and multiple-ascending dose studies in both healthy subjects and patients with depression. (Carhart-Harris et al., 2016; Griffiths et al., 2016). No significant adverse effects were noted. A microdose is typically about 10% of a “standard” dose (Anderson et al., 2019), and so we aim to administer 2mg of psilocybin, 10% of the dose commonly administered in clinical studies (Griffiths et al, 2016; Carhart-Harris et al., 2016). This dose has been used in prior research as a control condition with no discernable effects (Griffiths et al., 2016). Since it has been shown to be safe and asymptomatic in a clinical setting, it appears to satisfy the definition of a microdose, which is 1/10th the amount of higher doses. Additionally, many more survey respondents have reported using roughly this amount on average when they microdose (Anderson, Petranker, Rosenbaum, et al., 2019).

Together, this evidence suggests that the dose and dose frequency selected for this trial are within a dose range that is considered safe and tolerable in healthy subjects and patients.

2.3 Statement of Compliance

The trial will be conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, Health Canada Division 5, Declaration of Helsinki, and applicable Standard Operating Procedures (SOPs). The trial will be conducted under an IRB reviewed and approved protocol and conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; each subject will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

3.0 Protocol Objectives

The overall objective of this study is to use standard clinical measures to explore the effects and safety of low doses of psilocybin on Individuals with MDD. The purpose of this trial is to determine if psilocybin can improve depressive symptoms in this population.

3.1 Primary Objective

The primary objective of this study is to evaluate the effect of psilocybin on depressive symptoms in individuals with mild to moderate Major Depressive Disorder (MDD) , as measured by a change in the SCID assessed at baseline, 4 weeks after initial experimental (i.e. psilocybin) session, 8 weeks after initial experimental session (i.e., after administering four or eight microdoses of psilocybin), and then longitudinally to assess how long it takes for the effects, if any, to wash out. We will also use the PHQ-SADS (Kroenke, Spitzer, Williams, & Löwe, 2010) as a means of assessing more generalized depressive symptoms.

3.2 Secondary Objectives

The secondary objective of this study is to evaluate the effect of psilocybin on the following constructs:

- Sustained attention, as measured by average accuracy on the Sustained Attention to Response Task (SART; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) and Metronome Response Task (MRT; Seli, Cheyne, & Smilek, 2013).

Changes in the following measures will be explored:

- Creativity, including: Unusual Uses Task (UUT), Remote Associates Task (RAT), Five Dot Problem (5-dot), and Insight Problems
- Sobriety, including: Finger-to-Nose test, Balance test, Standardized Field Sobriety Tests (SFST)
- General Self Efficacy (GSE)
- Dysfunctional Attitudes (DAS-A-17)
- Personality: Big Five Inventory II (BFI-II)
- Five Factor Mindfulness Questionnaire (FFMQ)
- Multidimensional Assessment of Interoceptive Awareness (MAIA-2)
- Psychedelic effects: Mystical Experience Questionnaire (MEQ30)
- Quick Inventory of Depressive Symptoms (QIDS)
- Social benefits, including: Mind in Eyes, and Others in the Self Scale (IOS)
- Alertness, including: Single Item Sleep Quality Scale (SQS)
- Chronic pain: Brief Pain Inventory, Short Form (BPI-SF)
- Well being: Quality of Life Inventory (QOLI)
- Qualitative reports on social benefit (QR-SB), self assessed symptoms and physiological discomfort (QR-SPD), and individual experience/subjective response (QR-SR).
- The Single-item sleep quality scale (SQS)

3.3 Safety Objective

The overall safety objective is to assess severity, incidence, and frequency of adverse effects (AEs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behaviour, and vital signs (refer to Section 9 of the protocol).

The following safety objectives will assess the safety of psilocybin:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Product (IP), such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.
2. Assess incidence of AEs by severity.
3. Assess incidence of Treatment Emergent AEs (TEAEs) by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and 3 days after IP administration.
5. Assess incidence of AEs by severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination.

6. Assess incidence of SAEs.
7. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.
8. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
9. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IP administration to end of each Experimental Session.

4.0 Protocol Design

4.1 Study Design Overview

This randomized, placebo-controlled, double-blind phase 2 clinical trial which crosses over to an open-label trial after four weeks It will assess the safety and effectiveness of psilocybin in participants with mild or moderate MDD . An overview of trial design is shown in Table 1.

The trial includes a 2-week Screening Period, a 1-week Baseline Assessment Period, a 4-week double-blind Treatment Period, a 4-week open label Treatment Period, a Follow-up Period and an invitation to participate in Long-term Follow-up indefinitely or until drop-out of study.

Potential participants will learn about the trial through our recruitment poster, which directs them to complete a pre-screening questionnaire.

Each participant will be prescreened for eligibility and the research study visits will be performed as detailed below:

- **Screening Period:** informed consent, eligibility assessment, and enrollment of eligible participants
- **Randomization/Treatment Period:** eight weekly Experimental Sessions and associated online tests 3 days after each Experiment Session
- **Follow-up Period and Study Termination:** weekly for 1 month after treatment completion. During this period symptom assessments will be conducted at weekly intervals alternating between the Quick Inventory of Depressive Symptomatology (QIDS) and phone interviews. A QIDS score of 12 will trigger a phone assessment with SCID.
- **Invitation to participate in Long-term Follow-up (LTFU) extension study:** interested participants will receive email invitations to fill out short surveys every 6 months for a period of 2 years after the final Experimental Session.

4.2 Planned Number of Participants

Approximately 100 subjects will participate in this trial so as to reach high confidence in the results obtained from the experimental design. Please see section 11.1 (Statistical Analysis) for additional reasoning. Each subject will receive a unique screening number which must be entered in a screening log that is maintained at the trial site. Under no circumstances will subjects screened in the trial be permitted to be re-screened for a second time in this trial.

4.3 Planned Duration of Study

The duration of the randomized study phase is from consent until completion of the Treatment Period which lasts approximately 8 weeks. Screening and Enrollment Confirmation are expected to take up to 1 week to complete. The minimum time that a participant who completes all study visits from Screening to Study Completion will be 9 weeks.

All participants will be invited to participate in the long term follow up which we refer to as “the extension study” below. The extension study visits will be done virtually every 6 months after the last Experimental Session to fill out short surveys via email, for a period of 2 years.

4.4 Randomization and Blinding Procedures

The trial will follow a simple randomization procedure and double-blinding procedure.

4.4.1 Randomization

After all applicable screening assessments have been performed, subjects who satisfy inclusion and exclusion criteria will be randomly allocated to one of the Treatment Arms. Bottles containing placebo or active drug with unique codes will be provided by the Licensed Dealer formulating the API and be delivered to a dedicated study personnel. Each subject will receive a unique screening number which must be entered in a screening log that will be maintained at the trial site. The screening number will be allocated sequentially in the order in which the subjects are screened. The results of each screening will be recorded in the screening log. Selected data for screened participants will also be entered in the eCRF, along with screening failure if the subject is not randomized to treatment.

4.4.2 Blinding

In order to reduce bias as much as possible, the trial is double-blind, keeping all subjects and the investigator blinded to the treatment. Participants and site staff will not be aware which group will be receiving psilocybin in the first four treatment sessions. .

A central, computer-based randomization procedure will be used to eliminate selection bias. To reduce the risk of breaking the blind, IP handling and administration will be carried out at the trial site by the abovementioned unblinded site personnel, independent of the Investigator and the Sponsor. The appearance of the psilocybin capsules, as well as the placebo will be identical for all treatment groups.

To further minimize bias in measuring effect, the data management team will analyze primary, secondary, and exploratory measurements. The data management team will be blinded to the visit number, number of treatments, and any data from the treating team after Baseline.

To ensure that all participants are treated in a similar manner, the site will be required to follow the protocol delineating the estimated amount of time per visit type and describing delivery of treatment. Participants will be held in the lab for the duration required to complete the tasks included in the Experimental Session and once they pass a sobriety test (approximately 5 hours). Video recordings of select Experimental Sessions may occur to verify adherence to the treatment manual if necessary, and for analysis of social interactions. If we decide video recording is necessary, a separate ICF will be submitted to the IRB.

The sponsor will ensure complete data collection for all participants, including those who discontinue treatment. The Site will be required to make and document a specific number of attempts to obtain follow-up data per protocol. All participants who receive at least one dose of IP and complete at least one follow-up assessment will be included in the final analysis.

4.4.3 Dispensing of Study Medication

Study medication will be labelled by the Licensed Dealer for participants to receive the active intervention and placebo intervention. The active and placebo interventions will be matched in appearance. The drug medications will be labelled with the active or placebo numbers, so that it can be dispensed to the right participants depending on which arm they are in the trial. The site will reach out via phone/email to the pharmacist to obtain the study medication. Only the randomizer and pharmacist members of the research team will know the identity of the drugs to be administered. These team members will not interact with study participants and will not be present during any drug administration sessions.

4.4.4 Procedure for Breaking Codes

In case of emergency, break envelopes identifying the treatment sequence for each individual participant will be kept with the DMF. The delegate pharmacist will also keep an electronic spreadsheet of allocations so that de-blinding can be performed rapidly in case of emergency.

A subject's treatment assignment should only be unblinded by the investigator when knowledge of the treatment is necessary for the immediate medical management of the subject or to ensure subject safety in the trial. The blinding will follow the ICH-GCP, Declaration of Helsinki and SOP for the procedures involved in unblinding. Unique codes will be assigned to each participant, such that, if it is necessary to break the code for one individual, the blindness of the investigator, with respect to the interventions received by other participants, will be preserved.

4.5 Treatment and Dosage Regimen

This study will compare the effects of psilocybin to placebo (maltodextrin) in Experimental Sessions. Doses of psilocybin given during an Experimental Session include 2 mg psilocybin capsules. Maltodextrin will be used as placebo since it is well-tolerated even in much larger doses than the one administered in this design and is normally used as an inert placebo in clinical trials (Whalley et al., 2008).

Table 2: Experimental Arms Description

Arm	Intervention/Treatment
Experimental: 8-week psilocybin microdose The Psilocybin Group will receive 2mg of psilocybin once weekly for 8 weeks at experimental sessions 1 through 8	Drug: PEX010
Experimental: Placebo First, Psilocybin Dose Second The Placebo-1st Group will receive an insert placebo once weekly for 4 weeks at experimental sessions 1 through 4 and then 2mg of psilocybin once weekly for 4 weeks at experimental sessions 5 through 8	Drug: PEX010 Placebo: Inert

4.6 Accountability Procedures for Investigational Product

Forms will be provided to track IP and placebo accountability and administration throughout the study. IP and placebo accountability and administration logs will be reviewed during routine monitoring visits. IP will be handled in accordance with all local, provincial, and federal regulations and forms pertaining to the use of controlled substances, and forms will be maintained by the appropriate controlled substance license holder or delegate. Each primary container label will contain a unique container number for the product assigned to a single Experimental Session. The lot number will be used to track IP administration in the Source Record and the product administration log.

The following records will be maintained at the site, in compliance with SOP and good documentation practices:

- Product delivery to trial site
- Product inventory at the site (product documentation and lot numbers)
- Product use by each participant
- Product return to sponsor or destruction of unused products

Records will include:

- Dates, quantities, batch/serial numbers, expiration dates
- Unique code numbers assigned to the investigational products and trial participants
- All shipping records will be kept

Study medication destruction will be done in batches and / or as per site / pharmacy SOPs.

The sponsor recommends the following templates can be used for drug accountability:

Table 3: Product Details

Protocol Title/Study Name:	
Investigational Product:	Dosage Form:
Protocol Number:	Dose/Unit:
Site Number/Name:	Lot #/IP ID#:

Qualified/Principal Investigator:	Expiry Date:
Manufacturer/Sponsor:	Associated Documents:

Table 4: Storage Details

Room/Location for Storage:	
Storage Requirements:	Ambient / 2-8^{o}C / Other _____

Table 5: Transaction Details

Date (dd/mmm/yyyy)		**Transaction Details**				**Balance of IP**			**Transaction Type Details**	
Date	**Received, Dispensed, Returned**	**Lot/ Bottle #**	**Participant ID**	**Performed by (initials)**	**Checked by (initials)**	**IN**	**OUT**	**TOTAL BALANCE**	***Location Received From**	***Location Returned To**

Accountability Record Complete: Yes Balance carried over to new record:

PI signature: _____ Date: ____/____/_____

*Location refers to where the drug was returned to when it left the sites responsibility; back to the sponsor, back to the research pharmacy or whether or not returned and destroyed on site.

Table 6: Participant Drug Accountability Log

Protocol Title/Study Name:	
Protocol Number:	Qualified/Principal Investigator:
Site Number/Name:	Product:
Licensed Dealer:	

Participant ID	**Treatment Assignment**

Dispensed to participant						**Returned by participant**			**Verified**		
Date Dispensed (dd/mmm/ yyyy)	*Dose*	*Quantity*	*Lot #/IP ID#*	*Expiry Date (dd/mmm/ yyyy)*	*Initials*	*Date Returned (dd/mmm/ yyyy)*	*Quantity*	*Received by (Initials)*	*Verified by (Initials)*	*Date Verified (dd/mmm/yyyy)*	*Comments*

PI signature: _____ Date: _____

Date (dd/mmm/yyyy)	**Transaction Details**						**Balance of IP**		**Destruction Type Details**
Date	Lot/ Bottle #	Participant ID	Performed by (initials)	Checked by (initials)	Performed by (initials)	Checked by (initials)	IN	OUT	

PI signature: _____ Date: _____

TEMPERATURE LOG

Room ____ -

(insert month) 2020

DATE	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Recorded Temperature (0C)								
Time								
24 hour minimum								
24 hour maximum								

Comments								
Recorder's Initials								
DATE	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Recorded Temperature (0C)								
Time								
24 hour minimum								
24 hour maximum								
Comments								
Recorder's Initials								
DATE	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Recorded Temperature (0C)								
Time								
24 hour minimum								
24 hour maximum								
Comments								
Recorder's Initials								
DATE	**25**	**26**	**27**	**28**	**29**	**30**	**31**	
Recorded Temperature (0C)								
Time								
24 hour minimum								
24 hour maximum								
Comments								
Recorder's Initials								

***PLEASE NOTE: The 24 hour Minimum and Maximum readings will only be recorded if available**

Room Temperature Thermometer: _____(Insert Type/Model #)

Thermometer Serial Number: _____ Calibration Expiry Date: _____

Room Temperature Thermometer is in room _____

Room Temperature Thermometer located _____ (insert where it is located in room).

Room Temperature Set Range for Drug Storage is _____ (I.E.20ºC to 25ºC).

4.7 Handling and Storage

The IP for each Experimental Session will be stored in a locked safe labeled with a protocol number, IP name, lot number, sponsor name, and a statement that the IP is restricted to clinical trial use only. All labels will comply with local and national regulations.

Psilocybin is a controlled substance and will be stored and handled in compliance with all relevant local and national regulations. In accordance with these requirements, the appropriate license holder or designee will be responsible for storing, dispensing, and administering Psilocybin. Temperature deviations will be as per site SOPs: medications will be quarantined, and the sponsor will be notified. Site will receive clearance from the sponsor prior to further drug dispensation.

5.0 Selection of Trial Population

5.1 Trial Population

This trial is designed to include 18 to 65 year old male and female participants with either an existing diagnosis of mild or moderate MDD or who receive this diagnosis during Screening. Participants who fulfill all of the inclusion criteria (Section 5.1.1) and none of the exclusion criteria (Section 5.1.2) are eligible for inclusion in the trial. Physicians from the QIs network will be used for patient referal.

5.1.1 Inclusion Criteria

Participants must:

- Have given written informed consent.
- Have a high school level of education.

- Be fluent in speaking and reading the predominantly used or recognized language of the study site (i.e. English).
- Be 18 to 65 years old.
- If of childbearing potential, must have a negative pregnancy test at study entry and must agree to use adequate birth control through 10 days after the last Experimental Session (refer to section 9.4.2 for contraceptive guidelines).
- Have a preexisting diagnosis of mild or moderate MDD or receive this diagnosis during screening.
- Agree that for one week preceding each psilocybin session, they will refrain from taking any nonprescription medication, nutritional supplements, or herbal supplement except when approved by the research team. Exceptions will be evaluated by the research team and will include acetaminophen, non-steroidal anti-inflammatory drugs, and common doses of vitamins and minerals with the exception of SAM-e, 5-HTP, L-tryptophan, and St. John's Wort.
- Agree to consume approximately the same amount of caffeine-containing beverage (i.e. coffee, tea) that they consume on a usual morning, before arriving at the research unit on the mornings of psilocybin session days. Caffeine consumption should not exceed more than ≥600mg/day. If the patient does not routinely consume caffeinated beverages, they must agree not to do so on psilocybin session days.
- Agree not to take any as needed (PRN) medications on the mornings of psilocybin sessions. Non-routine PRN medications for treating breakthrough pain that were taken in the 24 hours before the psilocybin session may result in rescheduling the treatment session, with the decision at the discretion of the investigators.
- Agree to refrain from using any psychoactive drugs, including alcoholic beverages, within 24 hours of each psilocybin administration. As described elsewhere, exceptions include daily use of caffeine.
- Must not be a habitual smoker.
- Agree to refrain from starting any new medications.
- Agree to refrain from starting any new complementary or alternative medicine practices (e.g., nutrition/diet modifications, supplements, meditation practice)
- Agree to refrain from starting any concurrent psychotherapy
- Are willing to comply with medication requirements per the protocol (refer to Section 6.2).
- Lifestyle Criteria; Refrain from working night shifts.
- Receiving any form of psychotherapy for Major Depressive Disorder

5.1.2 Exclusion Criteria

- The subject has participated in another investigational study within 60 days prior to the screening visit.
- Cardiovascular conditions: coronary artery disease, uncontrolled hypertension, angina, a clinically significant ECG abnormality (i.e. atrial fibrillation), TIA in the last 6 months, stroke, peripheral or pulmonary vascular disease (no active claudication).
- Blood pressure exceeding screening criteria described below:
    - Cardiovascular screening:
        - At the screening and randomization visit, blood pressure will be assessed to qualify to proceed in the trial. Each assessment occasion will involve one or more blood pressure readings. To qualify for the study, the participants blood pressure (mmHg) for at least one readings will not exceed 140 systolic and 90 diastolic.
        - Blood pressure (BP) will be taken while subjects are at rest and have been seated or supine for at least 5 minutes. The assessment will involve one reading. If the first reading differs by more than 5 mmHg, additional readings will be obtained and assessed 5 minutes later. During the BP assessment, the volunteer will be acclimated to the automated blood pressure monitoring equipment by repeatedly taking blood pressure with the device over the course of the trial.
- Epilepsy with a history of seizures.
- The subject has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
- The subject has a clinically significant history of head injury or head trauma per the judgement of the investigator.
- The subject has a history of cancer.
- Unstable medical condition, severe renal disease (creatinine clearance < 40 ml/min using the Cockcroft and Gault equation), hepatic disease (known history of liver disease, abnormal elevations in LFTs), or serious central nervous system pathology.
- Insulin-dependent diabetes; if taking oral hypoglycemic agent, then no history of hypoglycemia.
- Are pregnant (positive pregnancy test assessed at screening) or nursing, or are of childbearing potential and are not practicing an effective means of birth control (refer to section 9.4.2 for contraceptive guidelines).
- Currently taking on a regular (i.e. daily) basis any psychotropic medications including: investigational agents, psychoactive prescription medications (i.e. benzodiazepines), antidepressants, medications having a primary pharmacological effect on serotonin neurons (i.e. ondansetron), medications that are MAO inhibitors, opioid medications. If previously on antidepressants a minimum of five half lives must have passed from the

last dose of medication plus an additional seven days of stabilization before first administration of the drug.
- Use of steroids within the past two weeks.
- Current use of the following drugs will also meet exclusion criteria: ergot alkaloids, pimozide, midazolam, triazolam, lovastatin, simvastatin, fentanyl.
- Agree to refrain from using any psychoactive drugs, including alcoholic beverages within 24 hours of each drug administration. The exception is caffeine.
- Having had a previous negative experience with any psychedelic substance.
- Sensitivity to maltodextrin.

5.1.3 Psychiatric Exclusion Criteria

- Current or past history of meeting DSM-5 criteria for Schizophrenia, Psychotic Disorder, or Bipolar I or II Disorder.
- Having a first or second degree relative with schizophrenia, psychotic disorder (unless substance induced or due to a medical condition), or bipolar I or II disorder.
- Currently meets DSM-5 criteria for Dissociative Disorder, Anorexia Nervosa, Bulimia Nervosa, or other psychiatric conditions judged to be incompatible with establishment of rapport or safe exposure to psilocybin.
- Current or past history within the last 5 years of meeting DSM-5 criteria for a moderate or severe alcohol or drug use disorder (excluding caffeine and nicotine)**.**
- Use within 6 months of psychedelic substances.
- Elevated risk of suicide as determined by study psychiatrists using the Columbia-Suicide Severity Rating Scale (C-SSRS) and clinical judgment

5.3 Withdrawal Criteria

Participants may withdraw from the study freely at any time for any reason, without the need to justify their decision. However, the Investigator should record the reason for the participant's withdrawal, if possible. If the participants have completed one full Experimental Session and one full online Follow-up Session, which occurs 3 days after the Experimental Session, their data may still be used in the study. If participants drop out before completing either of these sessions they will not be included in data analyses.

Participants may also be withdrawn from the study if:
- The sponsor and the investigator agree that a participant should be withdrawn according to their best judgment. The sponsor and investigator must communicate with each other in such cases that the participant is at risk or not complying with the safety protocol.

- An adverse event or serious adverse event which in the opinion of the investigator requires discontinuation of the trial medication and further participation in the trial effects participants safety.
- Medical condition requiring discontinuation of the trial medication in the opinion of the investigator or sponsor.
- The participant is not complying with the assessments required at the study visits, and is not following the study inclusion and exclusion criteria, and/or is consuming restricted medications.
- The participant's medical status changes to include something in the exclusion criteria.
- Withdrawal of consent.

Any withdrawal determined by the investigator or sponsor will be explained to the participant. Any withdrawal must be fully documented in the eCRF, registered in the eCRF as discontinued, and followed by the Investigator and research site staff. If the reason for discontinuation is an adverse event, the specific event will be recorded in the eCRF, and an investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilized (refer to section 9 for timelines and definitions). If participants withdraw or are withdrawn, there will not be additional participants recruited.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the trial. The sponsor has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform participants and will ensure they receive appropriate therapy, follow-up, and Exit Plan. All procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor.

5.3.1 Follow-up for Withdrawn Subjects

If consent is given, participants will complete the same post-study and follow-up measures as the other participants. Follow-up will be completed every 6 months from the termination date for that particular participant. These participants will also have study results shared with them.

6.0 Treatment of Subjects

6.1 Treatment to be Administered

Participants will receive two 1mg dose of psilocybin-containing PEX010 (1mg) in size 3, Hydroxypropyl Methylcellulose (HPMC) Clear Capsules or an inert placebo once a week for 4 of the 8 weeks of the study duration. Participants will be asked to orally ingest (swallow) the capsule(s) with the aid of water. In the last 4 weeks, all participants will ingest two 1 mg dose of psilocybin-containing PEX010 (1 mg) capsules. Thus, p articipants will either take the psilocybin for the first 4 weeks (4 dosing days) or the last 4 weeks. This will be determined by

random assignment and will not be disclosed to participants until completion of the study including all subsequent follow-ups. A member of the research team will witness the research participant ingesting (swallowing) the study treatment capsule(s).

6.2 Concomitant Medications

The delegated research site staff will record concomitant medications during screening. All participants should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. Details of all concomitant medications will be recorded in the eCFR, along with the main reason for each prescription. All medications, over the counter (OTC) and prescription, will be collected from Screening through 7 days after the last Experimental Session. The research team will request information about any changes in medication at each contact. If during screening a participant is found to have recently discontinued any psychotropic drugs within the last 6 weeks, there will be a required washout period (at least five times the particular drug and its metabolites' half-live, plus one week for stabilization) before the first experimental session to avoid the possibility of any drug-drug interaction.

6.2.1 Allowed Medications

All herbal supplements, vitamins, nonprescription medications, and prescription medications must be reviewed and approved by the research team, and will include acetaminophen, non-steroidal anti-inflammatory drugs, and common doses of vitamins and minerals.

6.2.2 Prohibited Medications

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Psychoactive medications: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), reversible inhibitors of monoamine oxidase (RIMAs), tricyclic antidepressants (TCAs), noradrenaline-serotonin specific antidepressants (NaSSAs), monoamine oxidase inhibitors (MAOIs), other antidepressants, benzodiazepines), or any other psychotropic medications.
- Any other unlisted medication having a primary pharmacological effect on serotonin receptors (i.e. ondansetron).
- Opioid medications.
- Ergot alkaloids, pimozide, midazolam, triazolam, lovastatin, simvastatin, fentanyl. Use of marijuana, cannabidiol (CBD), St. John's Wort, 5-HTP, and other herbs and medicines with notable serotonergic effects are prohibited from Baseline to Study Termination.
- Any investigational treatments under study for depression are prohibited from use concurrent with this study.

If an SSRI, SNRI, MAOI or other antidepressant is used between Experimental Session 1 and Study Termination, the participant will be withdrawn from treatment and continue in follow-up.

6.3 Monitoring Subject Compliance

6.3.1 Dispensing and Accountability

The IP will only be dispensed to participants who meet the eligibility criteria and are randomized to a treatment group in the trial. The delegated research site staff(or the blinded designated personnel) will maintain a patient Drug Dispensing/accountability Log detailing the IP numbers and dates of IP used for each participant during the course of the trial. Dispensing will be captured in the eCRF and will be verified by a Monitor (a Sponsor representative) during the trial and signed off by the Investigator (or designated personnel).

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant federal and provincial regulations.

6.3.2 Assessment of Compliance

The IP will be administered to the participant by authorized trial staff at the trial site and the procedure will be documented in the appropriate Dispensing Log. The IP will be stored securely per regulations.

It will be ensured that participants swallow the appropriate capsule(s) via visual inspection and participants will be held in the lab for the duration required to complete the tasks included in the Experimental Session and once they pass a sobriety test (approximately to 5 hours). This period of time is appropriate for the completion of experimental session assessments and to ensure physiological and psychological levels are within a typically functioning range for such a dose as demonstrated by Hasler et. al. (Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004). Several sobriety tests will be administered before participants leave the lab for safety reasons and as an exploratory measure.

7.0 Assessment of Efficacy

7.1 Primary Outcome Measure and Reliability

<u>PHQ-SADS (Patient Health Questionnaire Somatic-Anxiety-Depression)</u>

The PHQ-SADS is a 32-item self-report subset of the full PHQ designed to detect the co-occurrence of somatic, anxiety, and depressive symptoms (the SAD triad). The PHQ-SADS includes the PHQ-9, GAD-7, and PHQ-15 (Kroenke, Spitzer, Williams, & Löwe, 2010). The PHQ-9

is a 9-item depression module taken from the full PHQ. Items on the PHQ-9 are evaluated using a 4 point Likert scale (0=Not at all to 3=Nearly every day). Scores are used to classify depression severity as follows: None (0-4), Minimal (5-9), Moderate (10-14), Moderately severe (15-19), and Severe (20-27). The GAD-7 is a 7-item scale that uses DSM-5 criteria to identify generalized anxiety disorder (GAD) and measures the severity of anxiety symptoms. Responders are asked to rate the frequency of anxiety symptoms on a 4-point Likert scale (0=Not at all to 3=Nearly every day). Scores on the GAD-7 of 5, 10, and 15 represent cutoff points for mild, moderate, and severe anxiety, respectively. The PHQ-15 consists of 15 questions that evaluate the severity of somatic symptoms and the presence of somatization and somatoform disorders. Items on the PHQ-15 are evaluated using a 3 point Linkert scale (0=Not bothered to 2=Bothered a lot). PHQ-15 scores of 5, 10, and 15 are used as cutoff points to classify somatic symptoms as either low, medium, or high, respectively. It can be completed in 4-5 minutes.

SCID-5 (Structured Clinical Interview for DSM-5)

The Structured Clinical Interview for DSM-5 (SCID) was designed as a brief structured diagnostic interview for the major psychiatric disorders in the DSM-5 (First & Williams, 2020). Validation and reliability studies have shown that the psychometric indicators of this version of the instrument is in accordance with the quality parameters of the health status instruments (Osório et al., 2019). This study will use the SCID screening questions, and participants who respond positively to any of the questions will be excluded from the study and encouraged to seek mental health advice.

7.2 Secondary Outcome Measure

SART (Sustained Attention Reaction Task)

The SART has been widely used in the psychological literature as a measure of vigilance, the ability to sustain attention over a prolonged period of time. The duration of each testing block is approximately 4.3 minutes. Participants view a monitor on which a random series of single digits are presented at a regular rate (1 per 1.15 seconds, for a total of 225 presentations). The test uses a Go/No-go paradigm: the participant is instructed to press a response key following each presentation with the exception of a designated “no-go” digit. The no-go digit is presented with a frequency of 1 in 9. Participants are asked to give equal importance to accuracy and speed. Scoring is assessed by recording reaction time and error rate (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). Participants will undergo four blocks back to back, for a total of 20 minutes.

UUT (Unusual Uses Task)

The Unusual Uses Task (UUT) is a commonly used task to measure divergent thinking processes in creativity, the ability to generate novel solutions to a problem. The task requires that participants generate creative uses for mundane objects (Silvia, 2011). The UUT instructions

emphasize the importance of original responses, reading “Please try and think of the most unusual, creative, and uncommon uses you can imagine” (Harrington, 1975). Participants are asked to give as many responses as they can for each of two items (e.g. brick, knife), allotted 1 minute for each. During analysis, responses are split into alphabetical lists to avoid within-participant biases. Responses are rated across three dimensions: uncommon, clever, and remote (Silvia et al., 2008).

RAT (Remote Associates Task)

The RAT is a commonly used measure of convergent thinking processes in creativity, the ability to find a specific solution to a problem (Mednick, 1962). Respondents are shown compounds (the cues) made up of three related words (e.g. show, life, row) and asked to identify a fourth word (the solution) that is associated with all three cues (e.g. boat). The solution can be related either by forming a compound word, a common phrase or by close semantic association. The task is scored with the provided answer counted as either correct or incorrect, and the total score is taken as the number of correct solutions. It has good psychometric properties and scores have been shown to correlate with other measures of convergent thinking, including insight problems and Raven’s Progressive Matrices (Lee, Huggins, & Therriault, 2014). Each problem is allotted one minute, and participants will complete 10 problems per session, completing the task in 10 minutes.

5-dot (Five Dot Problem)

The 5-dot problem is a measure of non-verbal fluency and divergent thinking processes in creativity, the ability to find novel solutions to a problem. The respondent is presented with a grid of rectangles; each contains a figure with 5 dots laid out symmetrically. They are instructed to produce as many different figures as possible in the 5 minute time limit by connecting the dots within each rectangle. The instructions state that not all of the dots need be used, and that participants should not repeat figures nor draw lines which do not connect the dots. At the start of the task respondents are shown a few examples of both good and bad solutions. The test is scored by counting: the number of figures, the number of repetitions, the number of rotated figures, the number of figures with added dots, the number of self-corrections, and the percentage of figures that are correct (Regard, Strauss, & Knapp, 1982).

Insight Problems

The insight problems are designed to assess creative problem solving requiring insight, commonly thought of as the “Aha” moment when a solution is found (Schooler, Ohlsson, & Brooks, 1993). They consist of a set of short word or diagrammatic problems that participants must solve. Two sets of insight problems will be used. Set A consists of the Triangle of Circles problem (“Given an upwards pointing triangle composed of circles arranged in rows composed of 1, 2, 3, and 4, respectively, make the triangle point downwards by moving only 3 circles”), the X-ray problem (“A doctor is faced with a patient who has a malignant, inoperable tumor in the middle of his stomach. The tumour must be destroyed, and there is a kind of ray that can be used to do so. If the rays reach the tumor all at once at a sufficiently high intensity, the tumor

will be destroyed. Unfortunately, at this intensity the healthy tissue that the rays pass through on the way to the tumor will also be destroyed. At lower intensities the rays are harmless to healthy tissue, but they will not affect the tumor either. What type of procedure might be used to destroy the tumor with the rays, and at the same time avoid destroying the healthy tissue?") (Loewenstein, Thompson, & Gentner, 1999), and the Horse Trading problem ("A man bought a horse for 60$ and sold it for 70$. Then he bought it back for 80$ and sold it for 90$. How much did he make in the horse trading business?"). Set B consists of the Pigpen problem ("Nine pigs are kept in a square pen, laid out in a 3x3 grid. Build two more square enclosures that would put each pig in a pen by itself"), the matchsticks problem (''Given six matches, make four equilateral triangles, with one complete match making up the side of each triangle.''), and the Train and Bird Problem ("Two trains 50 miles apart start towards each other at 25 mph. As the trains start, a bird flies from the front of one train towards the second. On reaching the second train the bird turns round and flies back to the first train, and so on until the trains meet. If the bird flies at 100 mph, how many miles will the bird have flown before the trains meet?"). Each problem has a unique solution that is scored as correct or incorrect. They can be completed in 5 minutes.

FTN (Finger-to-Nose Test)

The finger-to-nose test is a measure used in neurological examinations to assess impairments in motor functioning and coordination. The participant is instructed to stand facing the examiner with their feet together, arms stretched to the side and eyes closed. They are then instructed in turn to place their index finger of each hand to the tip of their nose. The examiner looks for evidence of tremor or difficulty controlling the range of motion (Swaine, Desrosiers, Bourbonnais, & Larochelle, 2005).

Balance Test (Romberg Test)

The Romberg balance test is used by clinicians in neurological examinations to detect impairments in functioning of the cerebellar (motor) and the vestibular (proprioception) systems. The participant is instructed to stand with their feet together on level ground, with arms at their sides and eyes open. The examiner stands facing the participant and observes them for about 20 seconds and notes any swaying or falling. The participant is then instructed to close their eyes and they are observed for their ability to maintain an upright posture. Impairment is judged by: failure to keep the eyes closed, a loss of balance requiring the feet to move, falling, or inability to stand upright with eyes with minimal swaying (Bickley, Szilagyi, & Bates, 2009).

Standardized Field Sobriety Tests (SFST)

The SFST are a set of three standardized tests that are widely used by law enforcement to assess suspected impairment in drivers. They have been shown to be sensitive to impairment by multiple categories of drugs, including alcohol, cannabis, stimulants, depressants, and opioids (Porath-Waller & Beirness, 2014). The tests are administered by a trained examiner who observes the participant for specified indicators of impairment. The tests that comprise the SFST are the Horizontal Gaze Nystagmus (HGN), the Walk-and-Turn (WAT), and the One-Leg Stand (OLS). HGN is an involuntary jerking of the eye that occurs when the eyes gaze to the side. For the HGN test, the participant is instructed to follow an object (e.g. pen) with their eyes as it is slowly moved from side to side. The examiner separately observes each eye for the presence or absence of three signs of impairment: lack of smooth pursuit, distinct nystagmus at maximum deviation, and nystagmus onset before 45°. In the OLS, the participant is instructed to stand with one foot approximately 15 cm off the ground and count aloud from 1,000 for 30 seconds.There are four indicators of impairment: swaying while balancing on one leg, using arms to maintain balance, hopping during the test, and putting the raised foot down. For the WAT, the participant is instructed to take nine steps, heel-to-toe, along a straight line. They are then to turn around in a manner that was demonstrated during the instruction and take another nine steps in the opposite direction. They are observed for eight signs of impairment: could not keep balance while listening to the test instructions, started the test before the instructions were completed, stopped walking during the test, did not touch heel-to-toe while walking, stepped off the line, used arms to maintain balance, took the incorrect number of steps, and turned improperly. Typically, participants are classified as impaired overall whenever they show impairments on two out of three SFST. The tests can be completed in 3-5 minutes.

GSE (General Self Efficacy Scale)

The GSE is an instrument designed to measure self-efficacy: the belief that one is capable of performing the behaviours necessary to produce a desired outcome. It is a self-report scale that consists of 10 items (i.e. “Thanks to my resourcefulness, I know how to handle unforeseen situations”) that are rated on a 4-point Linkert-type scale (ranging from 1=Not at all to 4=Exactly true). The total score is the sum of all items (range 10-40). It has good reliability with Cronbach’s $\alpha \geq 0.76$ (Schwarzer, Jerusalem, Weinman, Wright, & Johnston, 1995). It can be completed in 1-3 minutes.

DAS-A-17 (Dysfunctional Attitudes Scale, 17 item)

The DAS-A-17 is a short-version of the Dysfunctional Attitude Scale, a 40-item self-report scale designed to measure the presence and intensity of dysfunctional beliefs (de Graaf, Roelofs, & Huibers, 2009). Participants rate statements of beliefs (e.g., “If I fail at my work, then I am a failure as a person.”) on a 7-point Likert scale and the total score is the sum of the 17-items

(range: 17–119) with higher scores indicating more dysfunctional attitudes (Weissman & Beck, 1978). The DAS-A-17 includes a total score and two subscales: perfectionism/performance evaluation (11 items) and dependency (6 items). Reliability for total score was excellent (α = 0.91) and good for the subscales (perf: α = 0.87, dep: α = 0.85) (Anderson et al., 2019).

BFI-II (Big Five Inventory II)

The BFI-II is a major revision of the Big Five Inventory designed to assess personality. This model characterizes personality along five broad trait dimensions: Extraversion, Neuroticism, Conscientiousness, Agreeableness, and Openness. This five-factor model is the prevailing psychometric assessment of personality. Empirical studies have differentially linked trait dimensions of these five factors with the onset, severity, and progression of multiple psychiatric illnesses. The BFI-II revision was undertaken to integrate advances in the understanding and measurement of personality in the intervening years since the conception of the BFI. In the BFI-II the traits “Neuroticism” and “Openness to experience” have been re-labelled as “Negative emotionality” and “Open-Mindedness”, respectively (Soto & John, 2017). It is a self-report scale consisting of 60 short, descriptive items that are rated on a 5 point Linkert scale (1=Disagree strongly to 5=Agree strongly). It is divided into 15 4-item facet scales that aggregate into 5 12-item domain scales. It can be completed in about 10 minutes.

FFMQ (Five Facet Mindfulness Questionnaire)

The FFMQ is a 39-item self-report questionnaire that measures five facets of mindfulness: observing (8 items), describing (8 items), acting with awareness (8 items), non-judging (8 items), and nonreactivity (7 items). Respondents rate the degree to which each statement is true for them on a 5-point Linkert-type scale (1=never or very rare true 5=very often or always true; some items use a reverse-scoring). It is the most commonly used instrument to measure mindfulness (Danielson & Jones, 2017). The five facet scales have been shown to have adequate (αnonreactivity = 0.75), good (αnonjudging = 0.87, αobserving = 0.83, αacting with awareness = 0.87) and excellent (αdescribing = 0.91) reliability (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). It can be completed in approximately 10 minutes.

Multidimensional Assessment of Interoceptive Awareness - Version 2 (MAIA-2)

The Multidimensional Assessment of Interoceptive Awareness (MAIA) is a 37-item self report state-trait questionnaire designed to measure multiple dimensions of interoception. It was developed based on a factor analysis to improve the psychometric properties of the original MAIA (Mehling, Acree, Stewart, Silas, & Jones, 2018). The MAIA-2 assesses interoception using a 5 point Likert-type scale (0=Never to 5=Always; some items use a reverse scoring) comprised of 8 factor subscales: Noticing (4 items), Not-Distracting (6 items), Not-Worrying (5 items), Attention Regulation (7 items), Emotional Awareness (5 items), Self-Regulation (4 items), Body

Listening (3 items), and Trust (3 items). Cronbach alpha's for the eight subscales range from 0.64 to 0.83 (Mehling et al., 2018). It can be completed in 8-10 minutes.

Mystical Experience Questionnaire, 30-item (MEQ30)

The MEQ30 is a 30-item psychometrically validated scale that has been previously used to measure mystical-type experiences occasioned by psilocybin. It was developed and validated through a retrospective factor analysis of the 43-item MEQ. The MEQ was developed from the operational definition of a "mystical experience" (Stace, 1960). The four factors of the MEQ30 are: mystical, positive mood, transcendence of time and space, and ineffability. The mystical factor includes items from the internal unity, external unity, noetic quality, and sacredness scales of the MEQ43. Positive mood, transcendence of time and space, and ineffability each include items from their corresponding scales on the MEQ43. The items are rated on a 6-point Linkert-type scale, where 0="none; not at all," 1="so slight cannot decide," 2="slight," 3="moderate," 4="strong (equivalent in degree to any previous strong experience or expectation of this description)," and 5="extreme (more than ever before in my life and stronger than 4)." Scale scores are the sum of all responses on a given scale (Barrett, Johnson, & Griffiths, 2015). Typically, a "complete mystical experience" is defined as a score ≥60% of the total possible score on each subscale. The four factors of the MEQ30 displayed excellent reliability, calculated using Cronbach's alpha ($\alpha_{mystical}=0.97$, $\alpha_{positive\ mood}=0.92$, $\alpha_{trans.time/space}=0.86$, $\alpha_{ineffability}=0.90$) (Barrett et al., 2015). Factor loadings for the four-factor MEQ30 model show high loading of each item onto its intended factor, and support the internal validity of the instrument (Barrett et al., 2015).

Metronome Response Task (MRT)

The MRT was designed as a measure of sustained attention (Seli, Cheyne, & Smilek, 2013). During the task participants are presented with a series of auditory tones (one every 1300 ms) and instructed to respond with a button press synchronously to each presentation. The primary measure is the latency between the presentation of the tone and the participant's response. The task also assesses participant reports of mind wandering. They are presented with intermittent "thought probes" which require the participant to report on the content of their thoughts just prior to the onset of the probe (i.e. on task or task unrelated, such as future plans, lunch, etc.) (Seli et al., 2013).

Reading the Mind in the Eyes Test (Mind In Eyes)

The Mind in Eyes is a theory of mind task designed to assess deficits in social cognition. It has been shown to be sensitive to deficiencies seen in autism spectrum disorders (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The participant is shown 36 grey-scale photographs that depict only the eye region of the face. They are required to rate, by choosing among four words that describe mental states, what the person in the photo is thinking or feeling. Only one

of the answers is deemed correct, and the test is scored by counting correct and incorrect responses. It can be completed in 5 minutes.

Inclusion of Others in the Self Scale (IOS)

We hypothesize that Closeness is typically measured by the Inclusion of Others in the Self Scale (IOS, Aron et al., 1992), a one-item measure with 7 Venn diagram-like pairs of increasingly overlapping circles where one circle of 6 each pair represents the self and the other circle represents the relationship partner. This factor captures very broad conscious feelings of closeness with another person. Aron et al. found a Cronbach alpha of .93 for their sample. We will use six such diagrams, measuring the closeness participants feel currently with their: (1) Future self; (2) Past self; (3) Friends / Coworkers; (4) a stranger in the street; (5) Family (6) Romantic Partner.

SQS (Single Item Sleep Quality Scale)

The SQS is a self-report questionnaire designed to rate responders' quality of sleep over a 7 day period. It is a discrete visual-analog scale, scored from 0-10 (0=terrible, 1-3=poor, 4-6=fair, 7-9=good and 10=excellent). When producing a rating responders are asked to consider multiple components of sleep quality: how many hours of sleep they had, how easily they fell asleep, number of night-time awakenings (excluding times to go to the bathroom), how often they woke earlier than intended, and how refreshing their sleep was. It has been validated and found to have good concurrent construct validity against the Pittsburgh Sleep Quality Index and the Morning Questionnaire-Insomnia (Snyder, Cai, DeMuro, Morrison, & Ball, 2018).

Positive and Negative Affective Scale (PANAS)

The Positive and Negative Affect Schedule (PANAS: Watson, Clark, & Tellegen, 1988) will be used to measure state-level affective changes. The PANAS is a brief measure that consists of two 10-item mood scales. The scales contain words that describe different feelings and emotions (e.g., upset, enthusiastic), and participants were asked to indicate to what extent they felt each of the emotions *on that day*. Response options will range between (*very slightly or not at all*) to (*extremely*). Scores are summed across the 10 items to yield separate scores for NA and PA. The PANAS scales have acceptably high internal consistency reliabilities, with alphas ranging from .84 to .90 (Watson et al., 1988; Watson & Walker, 1996).

Qualitative Reports (QR-SB, QR-SPD, QR-SR)

The qualitative reports consist of sponsor-developed sets of open-ended questions. They are designed to collect short answer responses covering the respondents' experience in the trial over 3 domains: QR-SB (social perceptions and sharing, 3 questions), QR-SPD (self-assessed symptoms and physiological discomfort, 3 questions), and QR-SR (individual

experience/subjective responses, 8 questions). The full listing of the qualitative report questions is provided in Appendix A. Altogether they can be completed in about 15 minutes.

Brief Pain Inventory, Short Form (BPI-SF)

The BPI-SF is a self-report instrument commonly used to assess both pain intensity and pain interference in clinical and research settings (Cleeland, 1989). The BPI measures 4 items (current, worst, least, and average) of pain intensity over the past 24 hours on a 10-point scale (0=No pain to 10=Pain as bad as you can imagine), and pain interference (7 items: general activity, mood, walking ability, normal work, social relationships, sleep, enjoyment of life) for the past 24 hours. The average pain intensity is scored using cut-offs: no or mild pain (0-2), moderate pain (3-5), severe pain (6-10). Respondents are also asked about the location of pain, any current treatments or medications and the percentage of pain relief obtained from them. It has been shown to be sensitive to change in response to treatment (Tan, Jensen, Thornby, & Shanti, 2004) and has excellent reliability (Cronbach's $\alpha_{intensity}=0.85$, $\alpha_{interference}=0.88$) (Tan et al., 2004). It can be completed in 5 minutes.

Quality of Life Inventory (QOLI)

The QOLI is an instrument designed to assess satisfaction and importance across 16 domains that were theoretically derived from the life satisfaction construct. It consists of 32 self-report questions and covers the following domains: health, self-esteem, goals and values, money, work, play, learning, creativity, helping, love, friends, children, relatives, home, neighbourhood, and community (Frisch, 1994). For each domain, a specific definition is given that sets out what should be considered and the respondent is asked to rate how important the domain is to their happiness on a three point Linkert scale (0 =Not important, 1=Important, and 2=Extremely Important). The respondent is also asked to indicate how satisfied they are with the given domain on a six point Linkert scale (−3=Very Dissatisfied to +3=Very Satisfied). The score for each domain is given as the product of the two ratings. A QOLI Total score is also computed by dividing the sum of the domain scores by the number of non-zero domain scores. The QOLI Total score can range from −6 to +6. The QOLI has been shown to have acceptable psychometric properties (Cronbach's $\alpha=0.79$) (Frisch, 1994). It can be completed in 5 minutes.

GAD-7 (Generalized Anxiety Disorder 7-item scale)

The GAD-7 is a self-report 7-item scale that uses DSM-5 criteria to identify generalized anxiety disorder (GAD) and measures the severity of anxiety symptoms. Responders are asked to rate the frequency of anxiety symptoms on a 4-point Likert scale ranging from 0-3 in which a meaningful change is defined by 5 points or more (Kertz, Bigda-Peyton, & Bjorgvinsson, 2013).

Study visits may take between 4- 7 hours, where participants would arrive in the morning and have the treatment administered and other study visit assessments done. A break for lunch. .

Table 7 below shows a breakdown of the time it may take to complete the questionnaires and assessments, which is one part of study visit assessments.

Quick Inventory Of Depressive Symptomatology

The Quick Inventory of Depressive Symptomatology (QIDS) is a widely used clinical assessment tool designed to measure the severity of depressive symptoms in individuals. Developed by Rush et al. in 2003, the QIDS is a self-report questionnaire consisting of 16 items that assess various domains of depression, including mood, sleep disturbance, energy level, concentration, and suicidal ideation. The QIDS has demonstrated excellent psychometric properties, displaying high internal consistency (Cronbach's $\alpha = 0.86$) and test-retest reliability (intraclass correlation coefficient = 0.84) (Rush et al., 2003). Furthermore, it has shown strong concurrent validity when compared to other established depression rating scales, such as the Hamilton Rating Scale for Depression ($r = 0.84$) and the Montgomery-Asberg Depression Rating Scale ($r = 0.87$) (Rush et al., 2003). Due to its brevity, ease of administration, and sound psychometric properties, the QIDS has become a valuable tool for clinicians and researchers in assessing depressive symptomatology.

7.3 Safety Measures

C-SSRS (Columbia Suicide Severity Rating Scale)

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial (Sheehan, 1983) . It consists of a Lifetime version and a Since Last Visit version that assesses suicidal ideation, ideation intensity, and behavior. The C-SSRS consists of a series of questions, and can be administered during a face-to-face interview or over the telephone. The Lifetime version will only be administered at the initial Screening visit. All subsequent administrations will utilize the Since Last Visit version. The C-SSRS Intensity scale for Lifetime obtained a Cronbach's alpha of 0.93 and 0.94 for the Since Last Visit form, and Last Visit C-SSRS severity scores were positively correlated with the BDI "suicide thoughts" item (Leon, Olfson, Portera, Farber, & Sheehan, 1997).

Table 7: List of Assessments for Use in this Study

Assessment	Abbreviation	Chronbach's Alpha (α)	Measurement of	Time to Complete (mins)	Clinician Rated	Participant Self-Rated	Purpose of Assessment /Measure

Structured Clinical Interview for DSM-5	SCID	N/A	Major DSM diagnosis	20-40	X		Primary outcome
Patient Health Questionnaire Somatic-Anxiety-Depression Symptoms	PHQ-SADS	N/A	Somatic symptoms and co-occurrence of anxiety and depressive symptoms	4-5		X	Primary outcome
Quick Inventory of Depressive Symptomatology	QIDS-C	0.86	Depressive symptom severity	5-7	X		Additional outcome: many studies measure the impact of psilocybin using the QIDS (e.g., Carhart-Harris et al., 2016; 2017). This will allow us to measure participant outcomes compared to large-dose studies.
Columbia Suicide severity Rating Scale	CSSR	0.93	Suicide risk	20	X		Safety

Assessment	**Abbreviation**	**Chronbach's Alpha (α)**	**Measurement of**	**Time to Complete (mins)**	**Clinician Rated**	**Participant Self-Rated**	**Purpose of Assessment /Measure**
Sustained Attention Reaction Task	SART	N/A	Sustained attention/focus	20		X	Confirming findings from Anderson et al., (2019) and Petranker et al., (2020): microdosing is related to improved mood through better general attention ability.
Unusual Uses Test	UUT	N/A	Divergent creativity	5		X	Confirming findings from Prochazkova et al. (2018) and Anderson et al (2019): microdosing is related to improved mood through enhanced creativity.
Remote Associations Task	RAT	N/A	Convergent creativity	10		X	Confirming findings from Prochazkova et al. (2018) and Anderson et al (2019): microdosing is

							related to improved mood through enhanced creativity.
Five-Point Problem	5-dot	N/A	Creativity	1		X	Confirming findings from Prochazkova et al. (2018) and Anderson et al (2019): microdosing is related to improved mood through enhanced creativity.
Insight Problems	Insight	N/A	Creativity	5		X	Confirming findings from Prochazkova et al. (2018) and Anderson et al (2019): microdosing is related to improved mood through enhanced creativity.
Finger to Nose Test	FTN	N/A	Sobriety	1	X		Sobriety test to test whether people under the influence of a 2mg dose of psilocybin would be considered legally sober.
Romberg Test	Balance Test	N/A	Sobriety	1	X		Sobriety test to test whether people under the influence of a

							2mg dose of psilocybin would be considered legally sober.
Standardized Field Sobriety Test	SFST	N/A	Sobriety	3-5	X		Sobriety test to test whether people under the influence of a 2mg dose of psilocybin would be considered legally sober.
General Self-Efficacy Scale	GSE	0.76	Self-Efficacy	1-3		X	
Assessment	**Abbreviation**	**Chronbach's Alpha (α)**	**Measurement of**	**Time to Complete (mins)**	**Clinician Rated**	**Participant Self-Rated**	**Purpose of Assessment /Measure**
Dysfunctional Attitudes, 17-Item	DAS-A-17	0.91	Negative/harmful attitudes	4-5		X	Measures cognitive attitudes regarding depression, which will be instrumental to assess the utility of small doses of psilocybin for cognitive therapy.
Big Five Inventory-2	BFI-II	N/A	Personality traits	10		X	Replicating the results of Anderson et al. (2019) and Polito and Stevenson (2019) in a lab setting to assess whether psilocybin-

							dependent personality changes are related to mood improvement.
Five Facet Mindfulness Questionnaire	FFMQ	N/A	Mindfulness qualities	10		X	Pursuing the hypothesis of Payne et al. (2021) this measure will be used to assess the way in which mindfulness mediates the relationship between psilocybin-use and improved mood.
Multidimensional Assessment of Interoceptive Awareness, Version 2	MAIA-2	.64-.83	Introspective abilities and awareness	8-10		X	the MAIA links attentional attitudes towards interoceptive signals with emotion regulation and mental health. Reported psychedelic effects include altered mood which has foundations in interoception; MAIA therefore presents an opportunity to examine whether microdosing improves a person's

							relationship with interoceptive signals as a mechanism of action.
Mystical Experience Questionnaire, 30-Item	MEQ30	.86-.97	Psychedelic effects	5-7		X	This measure will be used to quantitatively assess whether participants break blind.
Metronome Response Task	MRT	N/A	Sustained attention/focus	20		X	Confirming findings from Anderson et al., (2019) and Petranker et al., (2020): microdosing is related to improved mood through better attention ability. Importantly, this measure includes a musical aspect.
Assessment	**Abbreviation**	**Chronbach's Alpha (α)**	**Measurement of**	**Time to Complete (mins)**	**Clinician Rated**	**Participant Self-Rated**	**Purpose of Assessment /Measure**
Reading the Mind in The Eyes	Mind in Eyes	N/A	Social capacities	5			Confirming the findings of Petranker et al. (2022) that mood improvement following

							microdosing is mediated by an increased cognitive sense of connectedness.
Inclusion of Others in Self Scale	IOS	0.93	Social capacities	5		X	Confirming the findings of Petranker et al. (2022) that mood imporvement following microdosing is mediated by an increased emotional sense of connectedness.
Singe Item Sleep Quality Scale	1-item SQS	N/A	Sleep quality	1		X	Verifying anecdotal reports from Fadiman and Korb (2019) that microdosing improves sleep.

Assessment	**Abbreviation**	**Chronbach's Alpha (α)**	**Measurement of**	**Time to Complete (mins)**	**Clinician Rated**	**Participant Self-Rated**	**Purpose of Assessment /Measure**
Qualitative Reports of Social Benefits, Symptoms of Physical Discomfort and Subjective ResponsesPsychomotor Vigilance Task	QR-SB, QR-SPD, QR-SRPVT	N/AN/A	Subjective experiencesPsychomotor vigilance	1510		XX	Many of the experiences of participants in psychedelics trials cannot be captured in quantitative measures; the purpose of these measures is to qualitatively assess participant experience.Exploratory measure
Brief Pain Inventory, Short FormQualitative Reports of Social Benefits, Symptoms of Physical Discomfort and Subjective	BPI-SFQR-SB, QR-SPD, QR-SR	.85-.88N/A	Pain intensity and interferenceSubjective experiences	515		XX	Verifying anecdotal reports from Fadiman and Korb (2019) that microdosing alleviates chronic pain.

Responses							The findings from this measure may significantly affect the way pain is managed.Many of the experiences of participants in psychedelics trials cannot be captured in quantitative measures; the purpose of these measures is to qualitatively assess participant experience.
Quality of Life InventoryBrief Pain Inventory, Short Form	QOLIBPI-SF	0.79.85-.88	Well-beingPain intensity and interference	55		XX	This is to replicate previous findings of improved well-being in those who microdose (Petranker et al., 2020; Fadiman 2018; Polito & Stevenson,

							2019). Replicating these findings in a lab study is crucial.Verifying anecdotal reports from Fadiman and Korb (2019) that microdosing alleviates chronic pain. The findings from this measure may significantly affect the way pain is managed.
Quality of Life Inventory	QOLI	)0.79	Well-being	5		X	This is to replicate previous findings of improved well-being in those who microdose (Petranker et al., 2020; Fadiman 2018; Polito & Stevenson, 2019).

							Replicating these findings in a lab study is crucial.
Sphygmomanometer reading	BP	N/A	Blood pressure	1-2	X		Baseline and descriptive information
Generalized Anxiety Disorder 7-item scaleSphygmomanometer reading	GAD-7BP	N/AN/A	Symptoms of anxietyBlood pressure	1-31-2	X	X	Some people who microdose report changes in anxiety levels (Anderson et al., 2019). We aim to replicate these findings.Baseline and descriptive information
Generalized Anxiety Disorder 7-item scale	GAD-7	N/A	Symptoms of anxiety	1-3		X	Some people who microdose report changes in anxiety levels (Anderson et al., 2019). We aim to replicate these findings.

8.0 Study Procedures

All assessments must be performed by qualified study staff delegated these duties on the Site Delegation Log. The sponsor will be notified of any delays or deviations to study procedures. If there are delays of more than a week between visits or contact, the site should assess the need for additional telephone contact with the participant to ensure safety.

8.1 Screening Period

8.1.1 Screening

Data from potential participants who do not pass telephone pre-screening will not be entered in the eCRF but reason of ineligibility will be documented on the Pre-screening Log. If deemed potentially eligible, the potential participant will receive a copy of the ICF for review and invited to the site for the screening visit. Site staff will explain and obtain written informed consent using the IRB-approved ICF. Written consent must be obtained prior to performing any tests or evaluations for the study. Discussion about the ICF may take place over a telephone call or at the first in-person visit. Prospective participants will be screened online according to an IRB-approved test battery to ascertain if they meet basic eligibility criteria. All individuals who are screened should be assigned a Screening Number and recorded on the Screening Log. At any time during Screening, if a potential participant is deemed ineligible, they will be classified as a Screen Failure, notified that they are not eligible for the study, and not be scheduled for any additional Screening assessments.

Medical and psychiatric records are required for the site physician to obtain a well-characterized medical history and assess eligibility.

Screening procedures must be completed but there can be some flexibility in timing and order of individual assessments within the Initial Eligibility and Medical Assessments categories below:

- Initial Eligibility, including measures, in-person discussions, and review of medical records.
- Medical Assessments, including labs, and physical exam.

-

The sponsor recommends the following order of assessments:

Initial Eligibility

Delegated site staff will:

- Must obtain informed consent of potential participants verified by signature on electronic informed consent form.
- Obtain demographic information (date of birth, gender, ethnicity).
- Complete or verify completion of documents for release of PHI as required by the Personal Health Information Protection Act (PHIPA).
- Administer the SCID to assess participants for Major DSM-5 diagnosis and severity.
- Administer the Lifetime C-SSRS to assess history of suicidal behavior and ideation.
- Direct participant to complete self-reported Screening measures.
- Review medical history to determine eligibility based on inclusion/exclusion criteria, relevant medical history, including history of current disease, other pertinent mental health history, and information regarding underlying diseases.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Assess childbearing potential and discuss requirements for adequate birth control for the duration of the study. A pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study during Baseline Assessment, and at study exit.
- Schedule study visits for participants who are eligible and available for the duration of the study.

Review results of all measures and discussions against eligibility criteria to assess initial eligibility. If deemed initially eligible, potential participants will be provided with instructions (and appointments, if applicable) for laboratory assessments. Some or all of these assessments may be contracted to third party vendors.

Medical Assessments

The physical exam must be performed by a qualified physician or trained delegate and lab assessments must be completed at a designated lab. Medical assessments will include:

- Blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature measurement will be performed by a QI delegate

- Height and weight collected by , which will be used to calculate Body Mass Index (BMI).
- Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen, and extremities will be performed by the QI or a QI delegate.
- Brief neurological exam (, sensory, motor, reflexes, and cerebellar function) will be performed by the QI or QI delegate.
- Perform two urine drug tests: one at the Baseline Assessment and the second at the fourth Experimental Session prior to the cross-over period. Participants will be informed that drug testing is random during consent and on the ICF.
- Clinical laboratory assessments, per Section 10.0 Clinical Laboratory Assessments. The clinical laboratory values will not be captured in the eCRF, but will be used to establish eligibility and will be kept with the participant's source record. Clinically significant abnormal values will be captured as medical history and as per investigator discretion for follow up and repeats of abnormal lab values may be done.

Additional visits (in-person, telemedicine or by telephone) may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the potential participant.

Once all results are obtained, the site team will review all medical assessments, notes from interviews and discussions, medical records, and measures against eligibility criteria. If, upon examination, there are questions raised about possible medical problems, the site physician will request additional tests, assessments, or measures as indicated. The investigator may also refer the participants for specialist follow up with participant permission if required if deemed initially eligible, . Study visits can or may be done in clinic or virtually via telemedicine. he site can provide technical support before the assessment if needed. The site staff will instruct the participant on how to access any virtually/telemedicine visits. For all research study visits the participants should have adequate internet access and be in a private and quiet space where they are comfortable talking about personal matters.

8.1.3 Enrollment

In advance of Enrollment, the site team will review all notes from Screening, medical assessments, notes, discussions, medical records, and measures against eligibility criteria.

At study onset, if a potential participant is eligible, the study team will contact the investigator for approval to enroll the potential participant. If a participant is approved by the investigator, the participant will be notified of enrollment by in-person or by telephone, then scheduled to come in for the first study visit. Once enrolled, AE/SAE collection requirements begin (refer to Section 11.0 Safety). Enrollment and the Baseline Assessment may take place on the same day.

8.2 Screening

During the screening the study RAs will:

- Inquire about concomitant medication use and medical history
- Measure vital signs: blood pressure, heart rate
- Perform pregnancy test for participants who are of childbearing potential
- Perform urine drug test (completed by LifeLabs)
- Administer the following tests:
    - Baseline symptoms
    - Sobriety tests
- Support participant in completion of Baseline self-reported measures:
    - PHQ-SADS
    - DAS-A-17
    - BFI-II
    - FFMQ
    - MAIA
    - 1-Item SQS
    - QOLI
    - PANAS
    - Qualitative questions
- Remind the participants of lifestyle modifications and refraining from using psychoactive or non-approved medications, prior to each Experimental Session per Section 5.2 Lifestyle Modifications.
- Schedule Enrolled participants for Experimental Session 1.

8.3 Treatment Period

During the Treatment Period, which occurs over a duration of 8 weeks, participants will complete eight Experimental Sessions. In the first 4 weeks, One group will receive psilocybin while the other will receive placebo during the Experimental Session. The crossover assignment is scheduled to take place at the Experimental Session during week 5 when both groups will receive the psilocybin capsule. The first Experimental Session will be scheduled one to two weeks after baseline QIDS.

Participants in the Psilocybin-first Group will receive 2 mg of psilocybin during each of the first 4 weekly experimental sessions. Each experimental session is followed by online assessments 3 days later. These assessments will consist of a series of questionnaires outlined in Section 7.5. For the remaining 4 weeks of the trial period the Psilocybin-first Group will continue to receive 2 mg of psilocybin during the weekly experimental session followed by the online assessments 3 days later.

Participants in the Placebo-first Group will receive an inert placebo during each of the first 4 weekly experimental sessions. Each experimental session is followed by online assessments 3 days later. These assessments will consist of a series of questionnaires outlined in Section 7.5. For the remaining 4 weeks of the trial period the Placebo-first Group will receive 2 mg of psilocybin during the weekly experimental session followed by the online assessments 3 days later.

Experimental Session assessments and measures include the following and will be performed by delegated study research assistants:

- PHQ-SADS
- UUT
- RAT
- 5-DOT
- Insight (weeks 2,4,6,8)
- Sobriety Tests (FTN, Balance Test and SFST)
- GSE
- BFI-II
- FFMQ
- MAIA-2
- MEQ30
- MRT
- QR-SPD
- QR-SR
- QR-SRB
- IOS
- 1-Item SQS
- PANAS
- C-SSRS
- BP
- Body Temperature

Table 8: Outline of Treatment Procedure

Week	Day	Placebo First Group	Psilocybin First Group
0	Baseline (Day 0)	Participants will complete baseline measures including baseline symptoms, QIDS and SCID	

1	Experimental Session 1	Participants receive an inert placebo and are administered the Experimental Session assessments along with IOS and Mind in the Eyes	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments along with QR-IE, IOS and Mind in the Eyes
	Three days after Experimental Session 1	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS.	
2	Experimental Session 2	Participants receive an inert placebo and are administered the Experimental Session assessments (including Insight)	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments (including Insight)
	Three days after Experimental Session 2	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
3	Experimental Session 3	Participants receive an inert placebo and are administered the Experimental Session assessments	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments
	Three days after Experimental Session 3	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	

4	Experimental Session 4	Urine test for drug use occurs upon arrival. Participants receive an inert placebo and are administered the Experimental Session assessments and the following: ● SCID ● BFI-II ● MRT ● SART ● QOLI ● QR-IE ● IOS ● Mind in the Eyes	Urine test for drug use occurs upon arrival. Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments and the following: ● SCID ● BFI-II ● MRT ● SART ● QOLI ● QR-IE ● IOS ● Mind in the Eyes
	Three days after Experimental Session 4	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
5	Experimental Session 5	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments
	Three days after Experimental Session 5	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
	Experimental Session 6	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session

6		assessments (including Insight and PTV)	assessments (including Insight and PTV)
	Three days after Experimental Session 6	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB a(including Insight and P(including Insight)	
7	Experimental Session 7	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments
	Three days after Experimental Session 7	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
8	Experimental Session 8	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments and SCID	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session and SCID
	Three days after Experimental Session 8	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
Short-term followup	Weekly for 4 weeks	Participants complete the PHQ-SADS and QIDS over the phone.	

8.3.1 Experimental Sessions

Pre-IP administration

- On the day of the Experimental Session, the participant will arrive approximately 30 minutes prior to IP administration.
- The site team will ensure the participant has with all other requirements per Section 5.2 Lifestyle Modifications.
- The site team will inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements and record AEs as described.
- The site team will complete a concomitant medication review and ask the participant about recent recreational drug use, pregnancy status, and chance of pregnancy.
    - A positive response for current recreational drug use will be reviewed by the investigator and may be cause for delaying IP administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study, A positive response for pregnancy or possibility of pregnancy is cause for withdrawal from the protocol.
- Baseline blood pressure, body temperature, and pulse will be measured just prior to administration of the initial dose.

During the Experimental Session

- A qualified staff member will administer the initial dose of IP with an electrolyte-containing fluid in the morning.
- Electrolyte-containing fluids will be provided throughout the session.
- Blood pressure, body temperature, and pulse will be measured approximately 1.5 to 2 hours after the initial dose.
- Food will be provided during the last half of the session, approximately a 30-minute lunch break.
- The following assessments will be administered:
    - PHQ-SADS
    - UUT
    - RAT
    - 5-DOT
    - Insight
    - Sobriety Tests (FTN, Balance Test and SFST)
    - GSE
    - BFI-II
    - FFMQ

- MAIA-2
- MEQ30
- MRT
- QR-SPD
- QR-SR
- 1-Item SQS
- PANAS
- C-SSRS
- SCID

End of Experimental Session

- The delegated research staff will assess for AEs.
- The research team shall remain available to participants via 24-hour phone call, as needed.

8.3.2 Online Surveys After Experimental Sessions

After each Experimental Session, the following measures will be sent to each participant 3 days later, to be completed online ± 1 day:

- QIDS
- GAD-7
- DAS-A-17
- QR-SB
- PANAS

8.4 Follow-up Period and Study Termination

8.4.1 Follow-up Period

After the last Experimental Session, participants will enter follow-up/extension with no protocol required visits. During this period participants will be assessed weekly for four weeks. These assessments include symptom assessments conducted at weekly intervals alternating between the QIDS and PANAS, and include the PHQ-SADS every week. A QIDS score of 12 will trigger a phone assessment with HAMD-17 and SCID.

8.4.2 Study Completion / Termination

The Study Completion / Termination assessment will take place online 4 weeks after the last Experimental Session. Participants who have withdrawn from treatment but have continued for follow-up will also complete this assessment.

This assessment will:

- Inquire about any possible changes in health. Assess the participant's mental health and the status of any previously recorded AEs.
- Inquire about concomitant medication use.
- Provide and discuss a study Exit Plan
- Ask participants to enroll into the LTFU after the last experimental session, and review contact information for LTFU.
- Administer the following tests:
    - Qualitative Reports (see Appendix A).
    - Physical and mental symptoms.
- Actively support participant in completion of optional Study Termination self-reported measures:
    - PHQ-SADS
    - BFI-II
    - QOLI

After all Study Termination measures and assessments are completed, the participant is considered terminated from the study. The participant can resume normal everyday life. The study team will provide an Exit Plan, which may include a referral for additional medical or therapeutic care, as described in Section 8.4.2.2 Exit Plan. Eligible participants will be asked to participate in the LTFU extension study, described in Section 8.4.2.1 Long-Term Follow-up.

8.4.3 Long-Term Follow-up (LTFU) Extension Study

Upon completion of the study, defined as completing at least one Experimental Session and one QIDS assessment beyond Baseline, participants will be asked to join the LTFU extension study. The ICF for the extension study will be provided to eligible participants following Study Termination. The study will measure outcomes every 6 months after the last Experimental Session for a period of two years.

8.4.4 Exit Plan

At Study completion, participants will be provided with an Exit Plan. This Exit Plan will summarize treatments completed, current medications, and contact information for more information about the study if needed. Participants may request a referral for further therapeutic or medical care if appropriate. Enrolled participants who terminate the study early will be provided an Exit Plan at their last contact. Screen Failures will be provided a referral if requested. Participants of childbearing potential will perform another pregnancy test after their last study visit.

9.0 Assessment of Safety

9.1 Adverse Effects

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom or disease temporally associated with the administration of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

9.1.1 AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 9 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 9: AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.

Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

9.1.2 AE Relationship to Study Drug

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The relationship of an AE to the study drug should be assessed using the following guidelines in Table 10. In a clinical trial, the study product must always be suspect.

Table 10: AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose in the view of either the investigator or sponsor, results in any of the following outcomes:

- Results in death.
- Is life-threatening (the participant was at immediate risk of death from the event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.2.1 Adverse Events- Development of Severe MDE and/or Acute Suicidality

During the study and follow-up periods, should the subject report markedly worsening symptoms, acute suicidality, or CSSR category 1 or above,a study physician will assess the participant and based on clinical judgment may refer them for urgent psychiatric care and/or to an Emergency Department..

9.3 Recording and Reporting

Investigator Obligation to Report Serious Unexpected Adverse Drug Reactions (SUSARs) to Health Canada.

The investigator will inform Health Canada, in an expedited manner, of any serious unexpected adverse drug reaction, in respect of the study drug that has occurred inside or outside Canada [C.05.014]:

1. a) Where it is neither fatal nor life-threatening, within fifteen (15) days after becoming aware of the information;

2. b) Where it is fatal or life-threatening, within seven (7) days after becoming aware of the information. Within eight (8) days after having initially informed Health Canada of the fatal or life-threatening ADR, a complete report will be submitted as soon as possible. Follow-up reports of fatal or life-threatening reactions will include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

Each ADR which is subject to expedited reporting to Health Canada will be reported individually in accordance with the data element(s) specified in the Health Canada/ICH Guidance Document E2A: “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting”.

Expedited reports will be submitted for events that meet all of these three criteria: serious, unexpected and a suspected causal relationship.

1. Serious:

   Any untoward medical occurrence that at any dose:

   - Results in death,
   - Is life-threatening,
   - Requires inpatient hospitalization or prolongation of existing hospitalization,
   - Results in persistent or significant disability/incapacity, or
   - Is a congenital anomaly/birth defect.

2. Expectedness:

   An "unexpected" adverse reaction is one in which the nature or severity is not consistent with information in the relevant source document(s), such as the IB or Product Monograph. Until source documents are amended, expedited reporting will be submitted for additional occurrences of the reaction.

   Reports which add significant information on specificity or severity of a known, already documented serious ADRs constitute unexpected events. For example, an event more specific or more severe than described in the IB would be considered "unexpected" and should be reported (i.e., hepatitis with a first report of fulminant hepatitis).

3. Causality:

Causality assessment is required for clinical investigation cases:

- All cases judged by the reporting health care professional as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs and will be reported.
- Concomitantly, adverse reactions that are considered to be unrelated to the study drug by both the investigator will not be reported.

Further clarifications on ADR reporting requirements can be found on Health Canada's website:

E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting - Reminder for Sponsors, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/clinical-safety-data-management-definitions-standards-expedited-reporting-topic.html#a2A3

When submitting an ADR report to Health Canada, a complete ADR Expedited Reporting Summary Form (Form 01-03) and the CIOMS Form will be attached and as applicable be mailed or faxed to:

Therapeutic Products Directorate
Pharmaceuticals Fax: 613-941-2121

Adverse events that will be collected for the duration of the study are:

- Any adverse event related to withdrawal from the study.

Additional adverse events collected for seven days after each experimental session are:

- Common side effects.
- Exacerbations of mood symptoms.

The investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (i.e. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (i.e. death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting

documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

9.4 Pregnancy

9.4.1 Definition of Childbearing Potential

A participant is considered of childbearing potential if they were assigned female at birth and are post-menarche. A participant is considered not of childbearing potential if they are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), postmenopausal, or assigned male at birth.

9.4.2 Contraception Guidelines

Adequate birth control methods are required for participants of childbearing potential and include:

- An intrauterine device (IUD) which has been in use for at least 30 days.
- An intrauterine hormone-releasing system (IUS) which has been in use for at least 30 days.
- Non-oral hormonal methods, including injected, intravaginal, implanted, transdermal which have been used for at least 30 days.
- Oral hormones plus a barrier contraception (condom, diaphragm, or spermicide) which have been used for at least 30 days.
- Double barrier method (at least two of the following: condom, diaphragm, and spermicide).
- Vasectomized sole partner.
- Abstinence from penile-vaginal intercourse.
  o The reliability of abstinence should be evaluated carefully with the participant in relation to their general lifestyle. An additional acceptable birth control method should be discussed with the participant in case they decide to engage in penile- vaginal intercourse during the course of the study.

For questions about acceptable birth control methods, contact your study team.

9.4.3 Follow-up Requirements

Details of all pregnancies in study participants will be collected after Enrollment and collected through 10 days after the last Experimental Session. Pregnancies should be reported to the sponsor via telephone or email within 24 hours of site staff awareness.

In the event of a pregnancy, the participant will discontinue Experimental Sessions but may continue with non-drug Integrative Sessions, and Study Termination procedures.

The investigator will collect follow-up information on the participant and neonate and forward to the sponsor until the outcome of the pregnancy, which will be reported on an optional Pregnancy eCRF. Any termination, elective or spontaneous, will be reported. Abnormal pregnancy outcomes, such as spontaneous abortion, fetal death, stillbirth, congenital abnormalities, or ectopic pregnancy, will be reported as SAEs.

9.5 Rescue Medication and Risk Management

Recent reviews of the literature indicate that psilocybin is not associated with harm or damage to any organ or system in the body (Nichols, 2004, 2016); for more details see "Known Risks" section in this section or the protocol and sections of the Investigator's Brochure. Psilocybin can produce changes in blood pressure and heart rate, but these changes are not as strong or consistent as those seen with psychostimulants. High dose psilocybin can produce intense changes in mood, including periods of anxiety or panic (Griffiths et al., 2016; Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014). Both of these are transient in nature and do not last beyond the duration of the drug effects (Johnson et al., 2014). Surveys have suggested that the most commonly reported risk associated with microdosing psilocybin is that it is illegal, followed by relatively benign physiological side-effects such as temperature dysregulation, numbness/tingling, insomnia, gastrointestinal distress, and reduced appetite (Anderson, Petranker, Rosenbaum, et al., 2019; Hutten et al., 2019).

The investigators will discuss the possible effects of the study drug with participants during the Experimental Session prior to administration of the investigational product (IP). The research team will remain with participants for approximately five hours after drug administration, or until the participant is deemed stable by the psychiatrist on site. If appropriate, the participant will receive a rescue medication, but with a preference for supportive care first as described below. In addition, any study staff who have completed their training on the C-SSRS will be able to complete this psychological assessment. The follow-up provided to participants scoring for suicidal ideation will be performed by the study physician or another qualified mental healthcare professional.

If a participant exhibits signs of psychological distress, panic, or anxiety as described above, the investigators will first remind the participant that he or she has taken a psychoactive drug and that he or she can first stay with and work through the anxiety. Lorazepam and diazepam (IV, PO) will be available for on-site treatment of extreme acute anxiety if needed. Rescue medication will only be used if an individual is endangering him or herself or others, or at the discretion of the investigator. The use of prescribed rescue medications during an experimental session is contraindicated because it can interrupt effects of the IP on study measures, although

it would not be expected to cause any physical harm to the subject. Additional medications such as carvedilol, nitroglycerin, and IM haloperidol will also be available to participants in case of adverse events. Basic emergency equipment is available at the study site.

10.0 Clinical Laboratory Assessments

The investigator will confirm laboratory assessments gathered in screening for assessing eligibility. The investigator will use a list of normal ranges to conclude whether participants are eligible for the protocol.

The following laboratory assessments will be performed as a part of Screening:

- Serum electrolytes and metabolic profile
    - Alanineaminotransferase(ALT)/serum glutamic pyruvic transaminase(SGPT)
    - Albumin, serum
    - Alkaline phosphatase,serum
    - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT)
    - Bilirubin, total
    - Chloride, serum
    - Creatinine,serum
    - Glucose, serum
    - Potassium, serum
    - Sodium, serum
- CBC
    - Urinalysis
    - Thyroid-stimulating hormone (TSH)
- Pregnancy test for females of childbearing potential will be performed at the site
- Urinary drug test will be performed at the site

Laboratory assessments, with the exception of pregnancy tests , will be performed on site . Certificates and normal ranges will be stored in the site's Investigator Site File (ISF).

11.0 Statistical Considerations

11.1 Description of Statistical Methods

We will use the Bayes Factor Design Analysis approach (Schönbrodt & Wagenmakers, 2018) to determine the number of participants required to provide compelling evidence for meaningful changes to the primary and secondary measures. This criterion reflects our belief that these two measures test the constructs of interest most directly. We will use the sequential design with maximum participant approach to recruit additional participants until either (a) the Bayes

factor (BF) provides strong evidence for the null hypothesis (BF < 0.1) or alternative hypothesis (BF > 10), or (b) a total of 100 participants has been reached, or (c) we will not have sufficient funding for additional participants. We will compare the full linear regression model (outcome ~ condition + baseline) against the null model (outcome ~ baseline) to determine whether the BF has exceeded either threshold. Participants who fail to meet the criteria below will be excluded from the sequential sampling procedure and all analyses. They will be excluded if they complete fewer than 50% of the questionnaires on days attended. They will be excluded if they attend fewer than 2 experimental sessions.

We will fit the models using R and will report the following statistics that will be calculated from the posterior samples: beta estimate and its Bayesian 95% highest-posterior-density (HPD) interval and Cohen's d effect size. We will use null priors so as to allow the data to influence the outcome as much as possible. For each effect, we will also report the BF. BF = 1 indicates the data do not favor either the experimental or null hypothesis. BFs between 3 and 10 provide moderate evidence for the experimental hypothesis, whereas BFs between 0.3 and 0.1 provide moderate evidence for the null hypothesis. BFs greater than 10 or smaller than 0.1 provide at least strong evidence for the experimental and null hypothesis, respectively. We will also report frequentist probability values.

We will record and report any deviations from the plan. This study will be pre-registered on osf.io.

12.0 Study Governance

The sponsor, Psychedelic Research Consultants Inc., holds the primary responsibility of trial organization. This includes designing, initiating, managing, coordinating, continuing, and concluding the clinical trials. Psychedelic Research Consultants Inc. is tasked with maintaining the quality of study conduct through ongoing monitoring of data and participating in writing study publications.

12.1 Direct Access to Source Data/Documents

Source records contain all primary evidence of the existence of the participant and document all study procedures. Source records include but are not limited to medical records, measures, checklists, notes, emails, and laboratory reports. The secured U of T RedCap database will house all the source documents for this trial.

12.2 Quality Control and Quality Assurance

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.3 Ethics

This clinical study will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable Canadian Regulations, and the Centre for Addictions and Mental Health, The Principle Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except from necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The Protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

12.4 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Investigators and study staff will be trained prior to study start at the study site.

Data will be stored on the University of Toronto's REDCap servers, which are physically locked and access is restricted and monitored. All survey owners require two factor authentication to gain access to their individual surveys. Survey owners cannot see other surveys for which they

have no permission, and they have no access to anyone else's data. A limited number of system administrators have wider access, but their activities are highly regulated and documented.

Downloaded data will be downloaded to machines which are both password protected and physically under lock and key at the study trial location. The server uses 'full disk encryption', c.f., https://jumpcloud.com/blog/how-to-enable-full-disk-encryption-on-an-ubuntu-20-04-desktop and any access requires 2-factor authentication.

As for data storage, we will make all de-identified data open to the public in compliance with the *Tri-Agency Open Access Policy on Publications*, which requires that researchers: 1) deposit data into an appropriate public database immediately upon publication of results, and 2) retain all data sets associated with a given grant for a minimum of five years. This data will again be stored on the abovementioned secure encrypted drive. Deidentified data may be stored indefinitely on the pre-registration server / journal server, with no plans to delete.

For identifying information, we will destroy this information at the end of data collection. Identifying information (name, date of birth, contact info) will be deleted, and demographic info and study data will be attached only to a participant #. We will not be able to recover this information. Data of potential research participants who do not meet the inclusion/exclusion criteria will be immediately destroyed.

The study site will be monitored by site visits and telephone calls by representatives of the sponsor. In addition, critical data and systemic issues will be subject to centralized monitoring via the EDC system. The site will be monitored as appropriate for the rate of enrollment to comply with GCP guidelines and to ensure validity of study data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on eCRFs, source records, and IP accountability records. An eCRF collation will be completed for each participant enrolled within the EDC system. QIDS results may be shared with site staff. During or after the study, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, eCRFs, and other protocol documentation for on-site audit or inspection. Monitoring and auditing procedures will be supplied in a separate document. All data collected by the study will be stored for a period of 25 years as per the regulatory requirements. Site will notify the sponsor of the archiving location for all essential study documents.

There will be a site initiation visit, an interim monitoring visit after every 25 participants have completed study activities and a close out visit. The monitor may schedule more visits as needed.

12.5 Financial Disclosure

Investigators will adequately and accurately disclose financial interests to the sponsor prior to the study start, during the study if financial interests change, and 1 year after study completion. The sponsor will report necessary disclosures to the appropriate regulatory bodies.

12.6 Publication Policy

The sponsor recognizes the importance of communicating medical research and scientific data and their obligations to participants enrolled in a study and therefore, encourages publication of such material in reputable scientific journals and at professional and/or academic seminars or conferences.

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

Anonymized data will be stored indefinitely and access will be made available through the Open Science Framework repositories (https://osf.io/) as is becoming standard practice.

Identifying information will be removed before data is shared. This includes, but may not be limited to, names, date of birth, email addresses, telephone numbers, IP addresses, and any account numbers.

All participants may receive free copies of any published reports based on this data-set.

The above policy will be communicated to participants as part of the informed consent procedure.

12.7 Protocol Amendments

Any change to this Protocol will be documented in a Protocol Amendment, issued by the Sponsor or CRO, and agreed upon by the Investigator and the Sponsor prior to its implementation.

Protocol amendments will be submitted for approval to the IRB, in accordance with local regulations. An approval by the IRB is required for a substantial amendment, e.g. one which could affect the safety of the participants, or which entails a change to the scope/design of the trial.

Changes to the protocol to eliminate an immediate hazard(s) to trial participants may be implemented prior to IRB approval.

12.8 Trial Flow

	Screening	Treatment Period1				Treatment Period 2				Follow-up	Extension			
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Experimental Session		Exp Session 1	Exp Session 2	Exp Session 3	Exp Session 4	Exp Session 5	Exp Session 6	Exp Session 7	Exp Session 8					
Visit window(days)	± 7days	7days	7days	7days	7days	7days	7days	7days	7days	7-14-21-28 days	6mnth	6mnth	6mnth	6mnth
Subject related information and assessments														
Informed consent and demographics	x													
Childbearing potential	x													
Inclusion criteria	x	x	x	x	x	x	x	x	x	x				
Exclusion criteria	x	x	x	x	x	x	x	x	x	x				
Lifestyle modifications	x	x	x	x	x	x	x	x	x	x				
Medical history	x													
Conmedications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coffee use	x	x	x	x	x	x	x	x	x	x				

Tobacco use	x	x	x	x	x	x	x	x	x	x				
Enrollment														
	Screening	Treatment Period1				Treatment Period 2				Follow-up	Extension			
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Experimental Session		Exp Session 1	Exp Session 2	Exp Session 3	Exp Session 4	Exp Session 5	Exp Session 6	Exp Session 7	Exp Session 8					
Visit window(days)	± 7days	7days	7days	7days	7days	7days	7days	7days	7days	7-14-21-28 days	6mnth	6mnth	6mnth	6mnth
Randomization (enrollment confirmation)	x													
Vitals	x	x	x	x	x	x	x	x	x					
Body temperature	x	x	x	x	x	x	x	x	x					
Blood Pressure	x	x	x	x	x	x	x	x	x					
Body weight	x													
Height	x													
Lab assessments	x													
Urinalysis	x													

HIV serology	x													
% Carbohydrate deficient transferrin	x													

	Screening	Treatment Period1				Treatment Period 2				Follow-up	Extension			
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Experimental Session		Exp Session 1	Exp Session 2	Exp Session 3	Exp Session 4	Exp Session 5	Exp Session 6	Exp Session 7	Exp Session 8					
Visit window(days)	± 7days	7days	7days	7days	7days	7days	7days	7days	7days	7-14-21-28 days	6mnth	6mnth	6mnth	6mnth
Thyroid Function	x													
Safety														
Physical examination	x													
Pregnancy test	x	x				x								
Urine drug test	x	x				x								
AE/SAE	x	x	x	x	x	x	x	x	x	x				
Trial material														
Administration of trial product		x	x	x	x	x	x	x	x					
Dispensing visit		x	x	x	x	x	x	x	x					
Drug accountability		x	x	x	x	x	x	x	x					

	Screening	Treatment Period1				Treatment Period 2				Follow-up	Extension			
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Experimental Session		Exp Session 1	Exp Session 2	Exp Session 3	Exp Session 4	Exp Session 5	Exp Session 6	Exp Session 7	Exp Session 8					
Visit window(days)	± 7days	7days	7days	7days	7days	7days	7days	7days	7days	7-14-21-28 days	6mnth	6mnth	6mnth	6mnth
Questionnaires														
SCID	x				x				x					
QIDS*	x	x	x	x	x	x	x	x	x	x				
CSSRS	x	x	x	x	x	x	x	x	x					
PHQ-SADS	x	x	x	x	x	x	x	x	x	x	x	x	x	x
UUT		x			x				x					
RAT		x			x									
5 -DOT		x			x				x					
INSIGHT PROBLEMS		x			x				x					
FINGER NOSE TEST (FTN)	x	x	x	x	x	x	x	x	x					
ROMBERG TEST	x	x	x	x	x	x	x	x	x					

SFST	x	x	x	x	x	x	x	x	x					
	Screening	Treatment Period1				Treatment Period 2				Follow-up	Extension			
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Experimental Session		Exp Session 1	Exp Session 2	Exp Session 3	Exp Session 4	Exp Session 5	Exp Session 6	Exp Session 7	Exp Session 8					
Visit window(days)	± 7days	7days	7days	7days	7days	7days	7days	7days	7days	7-14-21-28 days	6mnth	6mnth	6mnth	6mnth
GSE		x	x	x	x	x	x	x	x					
DAS-A-17*	x	x			x				x					
BFI-II	**x**				x				x					
FFMQ	**x**				x				x					
MAIA-2	**x**				x				x					
MEQ30		x	x	x	x	x	x	x	x					
MRT		x			x				x					
SART		x			x				x					
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14

Experimental Session		Exp Session 1	Exp Session 2	Exp Session 3	Exp Session 4	Exp Session 5	Exp Session 6	Exp Session 7	Exp Session 8					
Visit window(days)	± 7days	7days	7days	7days	7days	7days	7days	7days	7days	7-14-21-28 days	6mnth	6mnth	6mnth	6mnth
Mind in Eyes		x			x				x					
IOS		x	x	x	x	x	x	x	x					
SQS	x	x	x	x	x	x	x	x	x					
PANAS*	x	x	x	x	x	x	x	x	x					
QR-SB*,QR-SPD,QR-SR	x	x	x	x	x	x	x	x	x		x	x	x	x
BPI-SF	x	x	x	x	x	x	x	x	x					
QOLI	x	x			x				x	x				

* will be sent 3 days after experimental session during the treatment period / ** this is 2- 4 hours prior to the study visit

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Appendix

Qualitative Report Questions (QR-SB, QR-SPD, QR-SR)

QR-SB

1. What effects do you predict that microdosing will have on your life?
2. Did you tell others that you were participating in this experiment? If so, whom, and how did they react?
3. Has anyone you know commented on any changes in your behaviour? Or have you had no comments from others?
4. Have you noticed any chances in your behaviour?
5. Have you started using psychedelics to macrodose or microdose outside of this study?
6. Do you think that you are in the experimental group or the placebo group? And how can you tell?

QR-SPD

1. How's your sleep been? Have falling asleep/waking up become different? Have your dreams changed?
2. Have you felt any changes to pre-existing symptoms? What's better and what's worse?
3. Have other people mentioned a change in your symptoms?

QR-SR

1. Have you noticed any changes in the way you think, feel, or behave? Anything subtle? Anything obvious?
2. Have you noticed anything that is the same in the way you think, feel, or behave? Anything stable that hasn't changed?
3. Given your experience so far, how do you feel about psychedelic microdosing?
4. Would you recommend psychedelic microdosing to others? Anyone in particular? Anyone that should avoid it?
5. What do you think about the legal status of psychedelics? Do you think they should be illegal, used as medicine, or legal for recreational use?
6. Have you experienced any negative outcomes related to participating in the study?
7. Overall, would you say that your experience participating in this study was a net negative or net positive for your life?
8. Is there anything else you want to report about your experience so far?