THE SAFETY AND EFFICACY OF PSILOCYBIN IN PARTICIPANTS WITH TYPE 2 BIPOLAR DISORDER (BP-II) DEPRESSION

IND:	137882
DRUG:	Psilocybin 3-[2-(Dimethylamino)ethyl]-1*H*-indol-4-yl dihydrogen phosphate
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STUDY SUMMARY

Title:	The Safety and Efficacy of Psilocybin in Participants with Type 2 Bipolar Disorder (BP-II), Depression
Rationale:	A recent open-label study of the effects of psilocybin in participants with treatment-resistant depression (TRD) showed rapid significant decrease of depressive symptoms after treatment with psilocybin coupled with psychological support. Over 40% of participants sustained response at 3 months. In this study, the aim is to assess effectiveness of 25 mg of psilocybin in patients with treatment-resistant type 2 bipolar depression
Target Population:	BP-II, current episode depressed
Number of Participants:	12 participants
Objectives:	The main purpose of this study is to determine the effect of Psilocybin at 25 mg. The intent of the primary analysis is to demonstrate efficacy of one therapeutic dose of 25 mg of psilocybin.

The primary objective of this study is to evaluate the efficacy of 25 mg of psilocybin under supportive conditions to adult participants with BP-II, current episode depressed, in improving depressive symptoms, as assessed by the change in the Montgomery-Asberg Depression Rating Scale (MADRS). Baseline is defined as the assessment score obtained on Day -1. The primary timepoint is Week 3; this variable will be analyzed for the change from Baseline to Day 1, and Weeks 6, 9, and 12.

The secondary objectives are:

- To assess the efficacy of psilocybin at 25mg in this population:
  - Proportion of participants with response defined as a ≥50% decrease in MADRS total score from Baseline to Week 3. This will also be assessed at Day 1 and at Weeks 1, 6, 9, and 12.
  - Proportion of participants in remission defined as the participants with a MADRS total score ≤10 at Week 3. This will also be assessed at Day 1 and at Weeks 1, 6, 9, and 12.
  - Proportion of responding participants who sustained a response up to Week 12 defined as those with ≥50% decrease in MADRS total score on or before Week 6 and remaining at Week 12.
- To evaluate the safety and tolerability of psilocybin in participants with BP-II, current episode depressed, based on tracking treatment emergent mania or hypomania as assessed by the Young Mania Rating Scale (YMRS), adverse events (AEs), changes in vital signs, and suicidal ideation/behavior (measured using the Columbia-Suicide Severity Rating Scale [C-SSRS]) score at all visits.

The exploratory objectives are:

- To evaluate the effects of psilocybin on quality of life and wellbeing, functioning and associated disability, cognitive function, and anxiety:

- Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) scale score change from Baseline to Week 3. This will also be assessed at Week 12.
- Functioning and associated disability in the Sheehan Disability Scale (SDS) score change from Baseline to Week 3. This will be also assessed at Week 12.
- Level of anxiety as measured using the change in Generalized Anxiety Disorder 7 item Scale (GAD-7) total score change from Baseline to Week 3. This will also be assessed at Week 12.
- Participant determined level of depression as measured using the change in Quick Inventory of Depressive Symptomatology Self Rated (QIDS-SR-16) total score from Baseline to Week 3. This will also be assessed at Day 1, and Weeks 1, 2, 6, 9, and 12.
- Psychosocial functioning and predictor of response durability as measured using the change in Work and Social Adjustment Scale (WSAS) from Baseline to Week 3. This will also be assessed at Week 12.
- The Positive and Negative Affect Schedule, Five Dimension Altered States of Consciousness questionnaire, and the Scale to Assess Therapeutic Relationship (Clinician and Patient version, respectively) will be assessed for correlation with the primary and secondary outcomes as possible predictors of response.

Study Design: This is a single center, open label, fixed-dose trial. The study population will include adult men and women, 18 to 65 years of age, with BP-II, current episode depressed.

Participants with BP-II are defined as those who meet the Diagnostic and Statistical Manual of Mental Disorders (5^{th} Edition; DSM-5) diagnostic criteria for recurrent episodes of depression and hypomania without psychotic features which have failed to respond to an adequate dose and duration of ≥ 2 pharmacological treatments for the current episode. Failure includes inadequate response to an adequate duration and dose or failure to reach an adequate dose and duration due to lack of tolerance. Augmentation counts as a second treatment.

Participants will be recruited primarily through the Sheppard Pratt Health System website and clinicaltrials.gov.

The majority of participants will have no prior exposure to psilocybin or so-called magic mushrooms. If the subject has a past exposure to psilocybin it has to be more than 12 months prior to Screening and not during the current depressive episode. .

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview (MINI), the Hamilton Depression Rating Scale (HAM-D-17), the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ), the Young Mania Rating Scale (YMRS) and the Columbia-Suicide Severity Rating Scale (C-SSRS). Those who meet the eligibility criteria will enter the screening period, which will last between 3 and 6 weeks. At the initial Screening visit (V1), the participant will also be evaluated with the QIDS-SR-16. Additionally, a medical history, an electrocardiogram (ECG), blood tests, and vital signs will be obtained. The participant will meet with the therapist on V1 to begin the psycho-education and preparation for the psilocybin experience.

During the screening period, participants who are on serotonergic medications will be expected to complete the taper at least 2 weeks prior to Baseline (V2). Participants will be given a choice of the tapering rate. During the tapering period all participants will be supported by the study clinician. The designated study nurse or coordinator will be in frequent contact with the participants to monitor for withdrawal and worsening of mood disorder symptoms. Participants will be assessed for suicidality with the C-SSRS and for emerging hypomania with the YMRS at each contact/visit.

Participants discontinuing serotonergic medication will be evaluated for safety at the clinic weekly for a minimum of 3 weeks prior to psilocybin administration to ensure safe discontinuation of current antidepressant therapy required by the protocol. Participants' family members and/or caregivers will be educated about the signs of worsening of depression and suicidality, and instructed on ways to contact the study team in case of significant worsening of depression. Any safety assessment visits during the screening period will be called V1a, V1b, etc. During these visits, the C-SSRS and any changes in medications since the previous visit will be obtained in addition to other assessments at the study clinician's discretion.

The day before psilocybin session, the participants will undergo a baseline assessment (3 to 6 weeks after initial Screening [V1] + 7 day window) that will consist of the HAM-D-17, MADRS, QIDS-SR-16, YMRS, C-SSRS, SDS, GAD-7, Q-LES-Q-SF, WSAS, vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential). Also, all participants will have a psychoeducation session with their therapist to discuss what to expect during the

psilocybin session. The therapist and a participant will review psychoeducational materials provided at the timetable of enrollment.

The psilocybin administration session (V3, Day 0) will last approximately 6 hours and will be supported by a trained therapist. A full description of the activities of the psilocybin administration session is found in the Study Manual. After the acute effects of the psilocybin pass, participants will be evaluated for safety and discharged home with a friend or a family member On Day 1 (V4), the day following psilocybin administration, participants will be seen in person for a safety check, assessment of suicidality, and to discuss their experience during the psilocybin session with the study therapist. **Participants are allowed to share insights that may arise during psilocybin experience.** All sessions between the therapist and the participant may be audio recorded for adherence monitoring and quality assurance. Audio and video recording of the sessions are subject to participant consent. Participants who do not consent to either or all recordings will <u>not</u> be excluded from the study. Participants will be asked to participate in integration sessions with the therapist on V4, V5, and V7 and a final check in on V10.

All participants will be asked to remain off their antidepressant medications for at least 3 weeks following the psilocybin session until the primary endpoint assessment, or longer. Rescue medications are allowed as noted in the protocol. Participants who restart their antidepressant medications during the first 3 weeks after the psilocybin treatment administration will be assessed for reasons of resuming their medications and followed until 12 weeks post psilocybin administration.

Participants will be seen at the clinic for Screening (V1), Baseline (V2, Day -1), Day 0 (V3, Dosing), Day 1 (V4), Week 1 (V5), Week 2 (V6), Week 3 (V7), Week 6 (V8), Week 9 (V9), and Week 12 (V10). If participants are contacted or seen at the clinic between the initial Screening (V1) and the Baseline (V2) visit, the visits will be labelled V1a, V1b, V1c, etc.

Eligibility Criteria:

<u>Inclusion Criteria</u>

Participants meeting all the following inclusion criteria at Screening (V1) should be considered for admission into the study

1. Signed ICF.
2. 18 years of age or older at Screening (V1)**; up to 65 at Screening.**
3. Must meet DSM-5 criteria for bipolar II depression episode based on medical records, clinical assessment and documented completion of the version 7.0.2 MINI.
4. HAM-D-17 (17-item) score ≥18 at Screening (V1) and at Baseline (V2). YMRS < 10 at V1 and V2.
5. Failure to respond to an adequate dose and duration of two or more pharmacological treatments for the current episode as determined through the MGH-ATRQ and the current episode >3 months. Failure includes inadequate response to an adequate duration and dose or failure

to reach an adequate dose and duration due to intolerance. Each augmentation strategy will be counted as an additional treatment.

6. Will have successfully discontinued all serotonergic medications at least 2 weeks prior to Baseline (V2).
7. Ability to complete all protocol required assessment tools without any assistance, and to comply with all study visits.

Exclusion Criteria

Participants meeting any of the following exclusion criteria at Screening (V1) will not be enrolled in the study.

Psychiatric Exclusion Criteria:

1. Current or past history of bipolar I disorder, schizophrenia, psychotic disorder (including substance induced or due to a medical condition), delusional disorder, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder, as assessed by medical history and a structured clinical interview (version 7.0.2 MINI).
2. Current cognitive behavioral therapy (CBT) that will not remain stable for the duration of the study. CBT cannot be initiated within 21 days of baseline.
3. Current (or < 1 year remission) alcohol or drug abuse as defined by DSM-5 at Screening (V1).
4. Significant risk of suicide based on the C-SSRS defined as answering "YES" to question 4 or 5 for "Suicidal Ideation" [past 1 month] on the Columbia-Suicide Severity Rating Scale, and/or answering "YES" to any question for "Suicidal Behavior" [past 3 months] on the Columbia-Suicide Severity Rating Scale) Or, if active suicidal activity or ideation during the current episode, eligibility will be determined at the investigator's discretion.
5. Depression determined to be secondary to other severe medical conditions.
6. Other conditions, personal circumstances and behavior judged to be incompatible with establishment of rapport or safe exposure to psilocybin.

General Medical Exclusion Criteria:

8. Women who are pregnant, nursing, or planning a pregnancy. Participants who are sexually active must agree to use a highly effective contraceptive method throughout their participation in the study. Women of child bearing potential must have a negative urine pregnancy test at Screening (V1) and Baseline(V2).
9. Cardiovascular conditions: recent stroke (< 1 year from signing of ICF), recent myocardial infarction (< 1 year from signing of ICF), uncontrolled hypertension (blood pressure > 140/90 mmHg) **or QTc > 450 msec**) or clinically significant arrhythmia within 1 year of signing the ICF.
10. Untreated uncontrolled OR insulin-dependent diabetes.
11. Known seizure disorder.
12. Positive urine drug screen for illegal or drugs of abuse **(to include but not limited to opiates, PCP, cocaine, amphetamines,**

methamphetamines, barbiturates and methadone) though cannabis for medicinal purposes or recreational use is permitted at V1 and V2. Any positive urine drug test will be reviewed with participants to determine the pattern of use and eligibility will be determined at the investigator's discretion in conjunction with thestudy physician.

13. Current enrollment in any investigational drug or device study or participation in such within 30 days of Screening (V1).
14. Current enrollment in an interventional study for depression or participation in such within 30 days of Screening (V1).
15. Abnormal and clinically significant results on the physical examination, vital signs, ECG, or laboratory tests at Screening (V1).
16. Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal or any other major concurrent illness that, in the opinion of the investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if he/she takes part in the study.

Investigational Product(s):

Dose: 25 mg psilocybin given at 5 capsules of 5 mg each

Primary Endpoint:

The primary endpoint is the change in MADRS total score from Baseline (Day -1) to 3 weeks (V7) from day 0 (V3).

Secondary Endpoints:

The secondary endpoints are:

- The proportion of participants with a response (defined as a ≥50% improvement in MADRS total score from Baseline) at Week 3 post psilocybin.
- The proportion of participants with remission (defined as a MADRS total score ≤10) at Week 3 post psilocybin.
- The proportion of participants who have a sustained response at Week 12.
- Time to event measures: restart antidepressant medication for any reason, restart medication for continuing depressive symptoms, and relapse from a previously recovered state (clinical judgement, supported by the QIDS-SR-16). Participants who withdraw from the study will be censored from the time to event analysis.

Exploratory Endpoints:

The exploratory endpoints are:

- Change from Baseline in the following:
  - Q-LES-Q-SF at Week 3
  - SDS at Week 3
  - GAD-7 at Week 3
  - QIDS-SR-16 at Week 3
  - WSAS at Week 3

Efficacy and Outcome Measures:

- MADRS
- QIDS-SR-16
- SDS
- GAD-7
- Q-LES-Q-SF

WSAS

Safety Assessments

- ECG
- Vital signs
- Blood test including liver function tests
- Suicide risk as assessed by the C-SSRS
- AEs and Serious AEs
- YMRS

Statistical Procedures

Analysis Sets

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

The modified intention-to-treat population will consist of all participants in the FAS that have at least 1 post dose assessment.

Sample Size Determination

This is an exploratory open-label study in a population not previously studied. Thus, no sample size calculation was done.

Primary and Secondary Efficacy Analyses

The primary efficacy endpoint (change from Baseline in MADRS total score at 3 weeks (V7) from day 0 (V3) will be evaluated with a mixed-effects model for repeated measures.

Exploratory Analyses

Change from baseline in continuous efficacy measures, including the QIDS-SR-16 scale and GAD-7 total scores at each point, will be analyzed based on last observation carried forward data using an analysis of covariance model, with treatment and study site as factors, and the respective baseline score as the covariate. The exploratory analyses for quality of life and wellbeing, functioning and associated disability, cognitive function, and anxiety are not hierarchical; there will be no correction for multiplicity in these analyses.

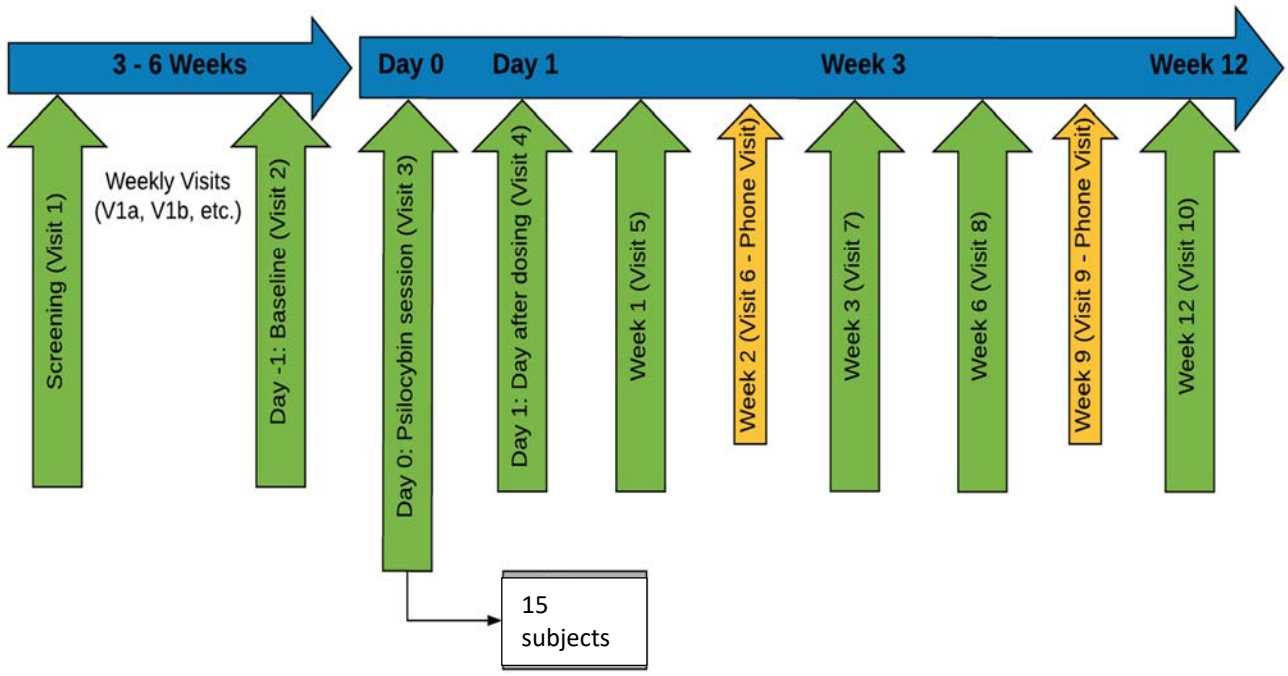
Scores for all efficacy endpoints, including scores of the Q-LES-Q-SF, will be summarized over time using descriptive statistics for all visits during the observation period.

The covariate selection process will be addressed in the Statistical Analysis Plan to be approved before any analyses are undertaken.

Safety Analysis

Safety analyses will be performed using data from the Safety Population. Safety will be evaluated based on AEs, vital signs, clinical laboratory assessments performed by a CAP/CLIA approved laboratory, and ECG findings.

577 **Study Schematic**



Green: In-Person Visits
Yellow: Remote Visits

578

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
5D-ASC	Five Dimension Altered States of Consciousness questionnaire
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bpm	beats per minute
BP-II	Bipolar Disorder (Type 2)
CBT	cognitive behavioral therapy
CFR	Code of Federal Regulations
CI	confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EBI	Emotional Breakthrough Inventory
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic Case Report Form
EIU	Exposure In Utero
EOS	End of Study
ET	early termination
FAS	full analysis set
GAD-7	Generalized Anxiety Disorder Scale
GCP	Good Clinical Practices
h	hours
HAM-D-17	Hamilton Depression Rating Scale
HDPE	high density polyethylene
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation	Definition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web-based Response System
kg	kilogram
L	liters
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
min	minute
MINI	Mini International Neuropsychiatric Interview
mL	milliliters
mmHg	millimeters of mercury
ng	nanogram
PI	Principal Investigator
PRN	*pro re nata*, as needed
PS	Prescreen
PT	Preferred Term
P-TRD	psilocybin for treatment-resistant depression
QIDS	Quick Inventory of Depressive Symptoms
QIDS-SR-16	Quick Inventory of Depressive Symptomatology – Self-Rated
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SDS	Sheehan Disability Scale
STAR-C	Scale to Assess Therapeutic Relationship – Clinician version

Abbreviation	Definition
TRD	treatment-resistant depression
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAS	visual analog scale
Worldwide	Worldwide Clinical Trials, Inc.
WSAS	Work and Social Adjustment Scale
YMRS	Young Mania Rating Scale

1 INTRODUCTION AND RATIONALE

The following is a summary of the information found in the current Investigator's Brochure (IB).[8]

1.1 Background

Psilocybin belongs to a class of drugs referred to as psychedelics ('mind-manifesting'). Specifically, psilocybin is considered a 5-hydroxytryptaminergic (serotonergic) psychedelic, along with other tryptamines such as dimethyltryptamine (DMT), ergolines such as lysergic acid diethylamide (LSD), and phenethylamines such as mescaline. Psilocybin was first isolated from psilocybin mushrooms by Hofmann in 1957, and later synthesized by him in 1958.[26] Psilocybin has been used in psychiatric research and in psychodynamic orientated psychotherapy from the early to mid-1960s up until it became a Schedule 1 substance in the United States (US) in 1970, and until the 1980s in Germany.[26,27] Research on the effects of psilocybin resumed in the mid-1990s, and it is currently the preferred compound for use in clinical research of 5 - hydroxytryptaminergic psychedelics,[5,14,19] because it has a shorter duration of action and suffers from less notoriety and stigma than other similar drugs.

1.2 Study Rationale

Carhart-Harris conducted an open-label feasibility study in 12 patients (6 men and 6 women) with moderate-to-severe, unipolar, treatment-resistant major depression (ISRCTN 14426797).[4] Each patient received 2 oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting. There was no control group. Psychological support was provided before, during, and after each session. The primary outcome measure was patient-reported intensity of psilocybin's effects. Patients were monitored for adverse events (AEs) during the dosing sessions and at subsequent clinic and remote follow-ups. Depressive symptoms were assessed using the 16-item Quick Inventory of Depressive Symptoms (QIDS); QIDS scores were obtained from week 1 to the 3 months following dosing. Psilocybin's acute psychedelic effects were detectable 30 to 60 minutes (min) after dosing, peaked 2 to 3 hours (h) after dosing, and subsided at least 6 h after dosing. Mean self-rated intensity (on a scale of 0-1) was 0.51 (standard deviation [SD] 0.36) for the low-dose session and 0.75 (SD 0.27) for the high-dose session. Compared to baseline, depressive symptoms were markedly reduced 1 week (means QIDS difference -11.8, 95% confidence interval (CI) -9.15 to -14.35, p=0.002, Hedges' g=3.1) and 3 months (-9.2, 95% CI -5.69 to -12.71, p=0.003, Hedges' g=2) after high-dose treatment. Marked and sustained improvements in anxiety and anhedonia were also noted. Psilocybin was well tolerated and no serious or unexpected AEs were reported. The AEs noted were transient anxiety (12/12 patients, 100%) during psilocybin onset, transient confusion or thought disorder (9/12 patients, 75%), mild transient nausea (4/12 patients, 33%), and transient headache (4/12 patients, 33%).

Bipolar depression remains the mood disorder condition with the fewest somatic treatment options. Current FDA approvals for bipolar depression are limited to several atypical antipsychotics and one anticonvulsant. Even within the framework of bipolar disorder, there is evidence to support a different treatment paradigm for those with a clear history of bipolar type I versus bipolar type II. While conventional wisdom has slanted toward lumping all bipolar depression into one treatment category, a recent study supports the notion that bipolar II patients may do just as well with or without mood stabilizers (Altshuler 2017 AJP)[43]. Given a gradually re-emerging evidence base for the use of psilocybin in a difficult to treat unipolar depressed group, there is an open question

as to whether this effect may carry over to patients with a difficult to treat mood disorder that includes a history of hypomania or low grade mixed states. This study proposes to determine if there is a signal for response as well as sufficient safety for the use of psilocybin in depressed patients who meet the diagnostic criteria for bipolar type II.

1.2.1 Pharmacokinetics

Psilocybin is detectable in plasma 20 to 40 min after oral administration of 0.224 mg/kg (10-20 mg total dose).[17] Orally ingested psilocybin is metabolized (dephosphorylated) in the liver, and primarily transformed into the active hydroxy metabolite, psilocin. Psilocybin is detectable in plasma 30 min after administration,[17,20,22,26] and psilocin is detectable in plasma 15 to 50 min after oral administration of 0.2 mg/kg psilocybin. Therefore, psilocybin is essentially a prodrug and psilocin represents the pharmacologically active agent in systemic circulation. The elimination half-life of psilocybin is 50 min.[22] Psilocin's half- life ranges between 2 and 3 h, and is detectable 6 h after oral administration.[17,22]Hasler et al. [17] and Lindenblatt et al.[22] reported similar but not identical findings, with peak levels of psilocin appearing between 80 to 105 min and psilocin half-life ranging between 2.25 h for 0.2 mg/kg and 2.7 h for 0.22 mg/kg. The majority, 80%, of psilocin in plasma was found to be in a conjugated form. Both psilocin (at 90-97%) and psilocybin (3-10%) are detectable in human urine, unmodified (only 3-10%) and particularly conjugated with glucuronic acid.[18] The majority of psilocin recovered in urine is excreted within 3 h after oral administration and is completely eliminated from the body within 24 h.[18]

1.2.2 Preclinical Pharmacology

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

Human psilocybin research has confirmed the importance of 5-HT_{2A} stimulation for the psychedelic effects of psilocybin and psilocin as the effects can be blocked by a 5-HT_{2A} receptor antagonist.[38] Reviews of the pharmacology of psilocybin is provided by Passie, and more current knowledge and perspective by Tyls et al.[26,37]

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

Although the literature on the effect of psilocin at the 5-HT_{2B} is somewhat contradictory, the most recent publication by Rickli et al. indicates that the half-maximal effective concentration (EC_{50}) for activation of the 5-HT_{2B} receptor is greater than 20 µM.[29] That concentration would generally be considered to be pharmacologically inactive *in vivo* because plasma concentrations would never reach 20 µM or greater after a single administration of psilocin. Brown et al. indicate that the maximal plasma concentration achieved after a single dose of 0.45 mg/kg in normal humans would not reach 200 nM (0.2 µM).[1] In any event, all studies suggest that chronic activation of the 5-HT_{2B} is necessary in order to invoke cardiac valvulopathy, and with a single administration there

should be no concern for that effect. With the EC_{50} reported by Rickli et al, even multiple administrations of psilocin would not be expected to be harmful. The valvulopathy induced by Fen-phen, or ergoline type anti-Parkinson agents, involved daily administration of the drugs over a significant period of time. Thus, there is no expectation that single use of psilocybin will be problematic.

1.2.3 Clinical Adverse Event Profile

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

The safety of psilocybin should be considered in terms of benefit and risk. Within the context of psilocybin administration in a controlled setting, a participant may report visual or auditory disturbances, feelings of unreality, altered sense of time, and other changes in mood or affect amongst other neuropsychiatric observations which have been previously described (see Table 4.1 of the current Psilocybin IB).[8] These effects are both expected, and may be a necessary component of therapeutic response. Investigators must follow regulatory guidance under 21 CFR 312.32(a) for AE reporting which addresses untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. However, because self-reports of intrapsychic events associated with psilocybin usage may be neither unfavourable nor unintended, an investigator may not regard the self-reports as an AE but rather as an essential product attribute for therapeutic response. The reporting of psilocybin associated observations as AEs should be informed by this context.

1.2.4 Potential Risk to Fetal Development

Reproductive toxicology studies have not been performed to establish risk to the fetus; however, the results of Ames test, the human lymphocyte micronucleus assay and the *in vivo* rat micronucleus study clearly indicate no potential for genotoxicity with psilocybin. It is recommended to prevent or eliminate such risk, if any, women should not be pregnant or lactating and should be using an effective method of birth control when using psilocybin.

1.2.5 Dosing Regimen

Carhart-Harris successfully evaluated 2 oral doses of psilocybin (10 mg and 25 mg) administered 7 days apart to patients with unipolar TRD; minimal AEs were reported in this study.[4] Work by the Griffiths group showed that under supportive conditions, psilocybin at doses of 20 to 30 mg/70 kg can dose-dependently occasion mystical-type experiences.[15]

2 STUDY OBJECTIVES

The main purpose of the study is to determine if there is a signal for efficacy of a psychedelic agent in BP-II, current episode depressed.

2.1 Primary

The primary objective of this study is to evaluate the efficacy of psilocybin (25 mg) administered under supportive conditions to adult participants with BP-II, current episode depressed, in improving depressive symptoms, as assessed by the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Baseline. Baseline is defined as the assessment score obtained on Day -1. The primary timepoint is Week 3; this variable will be analyzed for the change from Baseline to Day 1, and Weeks 1, 3, 6, 9, and 12.

2.2 Secondary

The secondary objectives are:

- To assess the efficacy of psilocybin in an open study on BP-II, current episode depressed:
  - Proportion of participants with response defined as a ≥50% decrease in MADRS total score from Baseline to Week 3. This will also be assessed at Day 1 and at Weeks 1, 6, 9, and 12.
  - Proportion of participants in remission defined as the participants with a MADRS total score ≤10 at Week 3. This will also be assessed at Day 1 and at Weeks 1, 6, 9, and 12.
  - Proportion of responding participants who sustained a response up to Week 12, defined as those with ≥50% decrease in MADRS total score on or before Week 6 and remaining at Week 12.
- To evaluate the safety and tolerability of psilocybin in participants with BP-II, current episode depressed based on Young Mania Rating Scale (YMRS) AEs, changes in vital signs, and suicidal ideation/behavior (measured using the Columbia-Suicide Severity Rating Scale [C-SSRS]) score at all visits.

2.3 Exploratory

The exploratory objectives are:

- To evaluate the effects of psilocybin on quality of life and wellbeing, functioning and associated disability, cognitive function, and anxiety on:

- Quality of life in enjoyment and satisfaction questionnaire-short form (Q-LES-Q-SF) score change from Baseline to Week 3. This will also be assessed at Week 12.
- Functioning and associated disability in the Sheehan Disability Scale (SDS) score change from Baseline to Week 3. This will be also assessed at Week 12.
- Level of anxiety as measured using the change in Generalized Anxiety Disorder 7 item Scale (GAD-7) total score change from Baseline to Week 3. This will also be assessed at Week 12.
- Participant determined level of depression as measured using the change in Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR-16) total score from Baseline to Week 3. This will also be assessed at Screening, Day 1, and Weeks 1, 2, 6, 9, and 12.
- Psychosocial functioning and predictor of response durability as measured using the change in Work and Social Adjustment Scale (WSAS) from Baseline to Week 3. This will also be assessed at Week 12.

3 STUDY ENDPOINTS

3.1 Primary

The primary endpoint is the change in MADRS total score from Baseline (Day -1) to 3 weeks post psilocybin.

3.2 Secondary

The secondary endpoints are:

- The proportion of participants with a response (defined as a ≥50% improvement in MADRS total score from Baseline) at Week 6 after the psilocybin session.
- The proportion of participants with remission (defined as a MADRS total score ≤10) at Week 3 post psilocybin.
- The proportion of participants who have a sustained response at Week 12.
- Time to event measures: restart antidepressant medication for any reason, restart medication for continuing depressive symptoms, and relapse from a previously recovered state (clinical judgement, supported by the QIDS-SR-16). Participants who withdraw from the study will be censored from the time to event analysis.

3.3 Exploratory

The exploratory endpoints are:

- Change from Baseline in the following:
  - Q-LES-Q-SF at Week 3
  - SDS at Week 3
  - GAD-7 at Week 3
  - QIDS-SR-16 at Week 3
  - WSAS at Week 3

3.4 Efficacy and Outcome Measures

Measures of interest include:

- MADRS
- SDS
- QIDS-SR-16
- GAD-7
- Q-LES-Q-SF
- WSAS

4 STUDY PLAN

4.1 Study Design

This is a single center, fixed dose, open trial. The study population will include adult men and women, 18 to 65 years of age, with BP-II, current episode depressed. Participants with BP-II, current episode depressed, are defined as those who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for recurrent episodes of major depressive and hypomanic episodes without psychotic features which have failed to respond to an adequate dose and duration of ≥ 2 pharmacological treatments for the current episode and the duration of the current episode is 3 months to 2 years. Failure includes inadequate response to an adequate duration and dose or failure to reach an adequate dose and duration due to lack of tolerance. Augmentation counts as a second treatment.

Participants will be recruited primarily from general practitioners and specialized psychiatric services.

The majority of participants will have no prior exposure to psilocybin or so-called magic mushrooms. Past exposure to psilocybin has to be more than 12 months prior to Screening and not during the current depressive episode.

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview (MINI), the Hamilton Depression Rating Scale (HAM-D-17), the Maudsley Staging Method (MSM), The Young Mania Rating Scale (YMRS), and the Columbia-Suicide Severity Rating Scale (C-SSRS). Those who meet the eligibility criteria will enter the screening period which will last between 3 and 6 weeks. At the initial Screening visit (V1), the participant will also be evaluated with the QIDS-SR-16. Additionally, a medical history, an electrocardiogram (ECG), blood tests, and vital signs will be obtained.

During the screening period, participants who are on serotonergic medications will be expected to complete the taper at least 2 weeks prior to Baseline (V2). Participants will be given a choice of the tapering rate. During the tapering period all participants will be supported by the study clinician during the discontinuation of any disallowed medications and their reinstatement.. The designated study nurse or co-ordinator will be in frequent contact with the participants to monitor for withdrawal and worsening of depression symptoms. Participants will be assessed for suicidality with the C-SSRS at each contact/visit. The study clinican will communicate any pertinent information via telephone or by fax to the patient's provider.

All participants will be evaluated for safety at the clinic weekly for a minimum of 3 weeks prior to psilocybin administration to ensure safe discontinuation of current antidepressant therapy required by the protocol. Participants' family members and/or

caregivers will be educated about the signs of worsening of depression and suicidality, and instructed on ways to contact the study team in case of significant worsening of depression. Any safety assessment visits during the screening period will be called V1a, V1b, etc. During these visits, the C-SSRS and any changes in medications since the previous visit will be obtained in addition to other assessments at the study clinician's discretion.

The day before psilocybin session, the participants will undergo a baseline assessment (3 to 6 weeks after initial Screening [V1] + 7 day window) that will consist of the HAM-D-17, MADRS, QIDS-SR-16, C-SSRS, SDS, GAD-7, Q-LES-Q-SF, WSAS, YMRS, vital signs, urinalysis, urine drug screen, and urine pregnancy test for women of childbearing potential. All participants will also have a psychoeducation session with their therapist to discuss what to expect during the psilocybin session at V1 and baseline V2. The therapist and a participant will review psychoeducational materials provided at the time of enrollment.

The psilocybin administration session (V3, Day 0) will last approximately 6 hours and will be supported by a trained therapist. A full description of the activities of the psilocybin administration session is found in the Study Manual. After the acute effects of the psilocybin pass, participants will be evaluated for safety and discharged home with a chaperone. On Day 1 (V4), the day following psilocybin administration, participants will be seen in person for a safety check, assessment of suicidality, and to discuss their experience during the psilocybin session. Participants should be allowed and encouraged to discuss insights that may otherwise be fleeting while the participant is under the influence of the drug. All sessions between the therapist and the participant may be audio recorded for adherence monitoring and quality assurance. Audio and video recording of the sessions are subject to participant consent. Participants who do not consent to either or all recordings will not be excluded from the study. Participants will meet with study therapist on V4, V5, V7 for integration sessions and a final check in on V10.

All participants will be asked to remain off their antidepressant medications for at least 3 weeks following the psilocybin session until the primary endpoint assessment, or longer. Rescue medications are allowed as noted in Section 8.5.4. Participants who restart their antidepressant medications during the first 3 weeks after the psilocybin treatment administration will be assessed for reasons of resuming their medications and followed until 12 weeks post psilocybin administration.

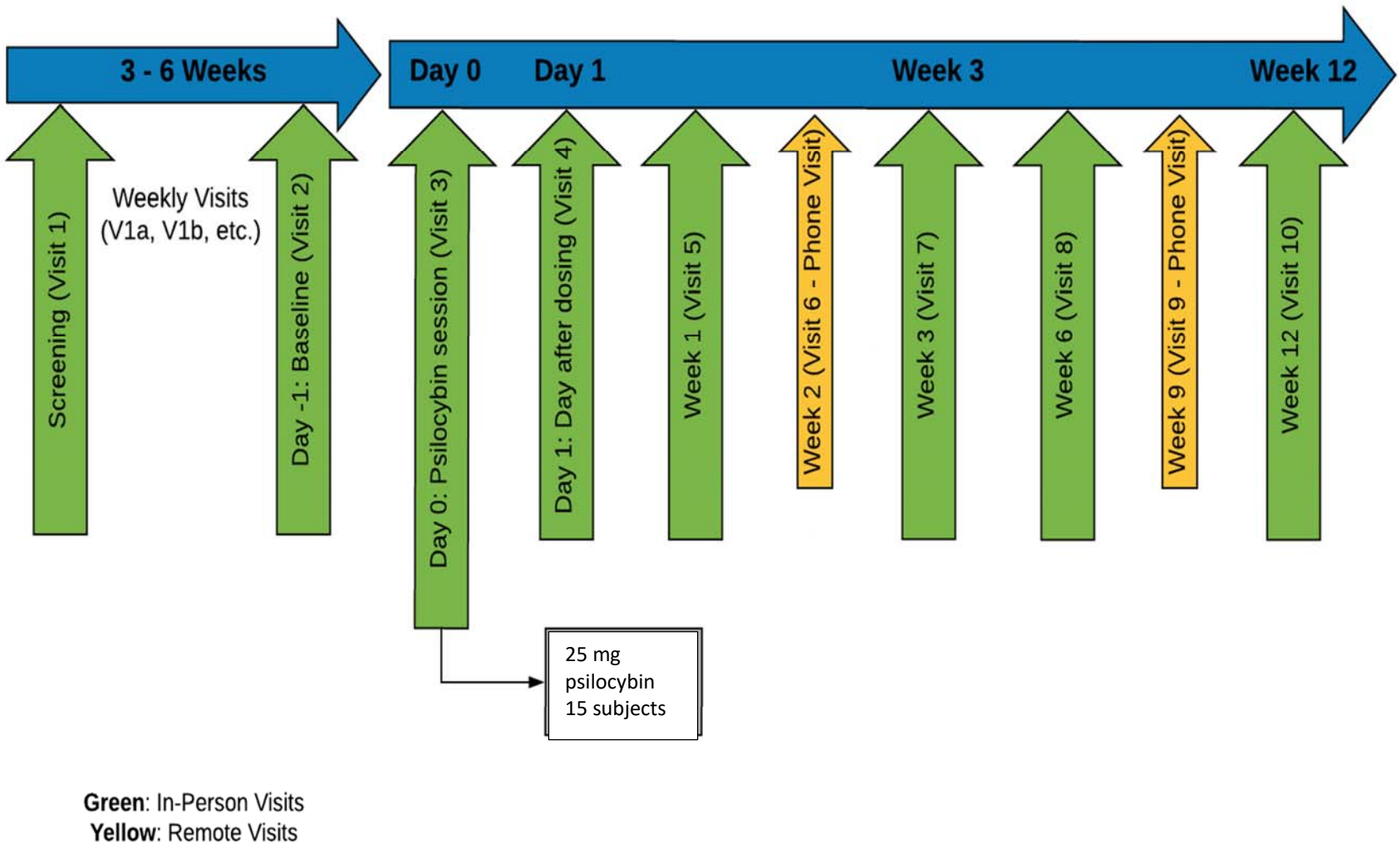
The treatment period will include 1 dose of 25 mg

Participants will be seen at the clinic for Screening (V1), Baseline (V2, Day -1), Day 0 (V3, Dosing), Day 1 (V4), Week 1 (V5), Week 2 (V6), Week 3 (V7), Week 6 (V8), Week 9 (V9) and Week 12 (V10).

If participants are contacted or seen at the clinic between the initial Screening (V1) and the Baseline (V2) visit, the visits will be labelled V1a, V1b, V1c, etc.

The study schematic is presented in Section 4.2 and the schedule of assessments is presented in Section 4.3.

4.2 Study Schematic



4.3 Schedule of Assessments

	≥3 weeks prior to Psilocybin Session			Time Post Psilocybin Session						
	Screen Visit[2] Day -21	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21	Week 6 Day 42	Week 9 Day 63	Week 12 Day 84 (ET)
Visit	1	2	3	4	5	6	7	8	9	10
Location of Visit[1]	Clinic	Clinic	Clinic	Clinic	Clinic	Remote	Clinic	Clinic	Remote	Clinic
Allowable Window		+ < 7 days		none	±1 day	±1 day	± 1 day	± 3 days	± 3 days	± 7 days
Clinic Assessments and Procedures										
Informed Consent	✓									
Medical History	✓	✓								
Inclusion/exclusion Criteria	✓	✓								
MINI	✓									
HAM-D-17	✓	✓								
MGH-ATRQ	✓									
C-SSRS[3] and YMRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓ [9]	✓						
Weight	✓									
ECG	✓									
Clinical laboratory tests [4]	✓									
Urinalysis[4]	✓									
Urine Drug Screen[4]	✓	✓								
Meet with Study Therapist	✓	✓	✓	✓	✓		✓			✓

	≥3 weeks prior to Psilocybin Session			Time Post Psilocybin Session						
	Screen Visit[2] Day -21	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21	Week 6 Day 42	Week 9 Day 63	Week 12 Day 84 (ET)
Visit	1	2	3	4	5	6	7	8	9	10
Location of Visit[1]	Clinic	Clinic	Clinic	Clinic	Clinic	Remote	Clinic	Clinic	Remote	Clinic
Allowable Window		+ < 7 days		none	±1 day	±1 day	± 1 day	± 3 days	± 3 days	± 7 days
Urine Pregnancy Test[6]	✓	✓								
Documentation of Birth Control to be used[7]	✓									
Psilocybin dose			✓							
Prior/Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AE/SAE			✓	✓	✓	✓	✓	✓	✓	✓
Participant Completed Assessments										
5D-ASC			✓[8]							
CEQ				✓			✓			
MEQ30				✓			✓			
EBI				✓						

	≥3 weeks prior to Psilocybin Session			Time Post Psilocybin Session						
	Screen Visit[2] Day -21	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21	Week 6 Day 42	Week 9 Day 63	Week 12 Day 84 (ET)
Visit	1	2	3	4	5	6	7	8	9	10
Location of Visit[1]	Clinic	Clinic	Clinic	Clinic	Clinic	Remote	Clinic	Clinic	Remote	Clinic
Allowable Window		+ < 7 days		none	±1 day	±1 day	± 1 day	± 3 days	± 3 days	± 7 days
Q-LES-Q-SF		✓					✓			✓
GAD-7		✓					✓			✓
QIDS-SR-16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SDS		✓				✓	✓			✓
WSAS		✓					✓			✓
MADRS		✓		✓	✓	✓	✓	✓	✓	✓

Abbreviations: 5D-ASC, Five Dimension Altered States of Consciousness Questionnaire; AE, adverse event; CEQ, The Challenging Experience Questionnaire; CRP, C-reactive protein; DSM-5 Diagnostic and Statiscal Maual of Mental Disorders (5th edtion); EBI, Emotional Breakthrough Inventory; ECG, electrocardiogram; ET, early termination; GAD-7, Generalized Anxiety Disorder 7; h, hour(s); HAM-D -17, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Scale; MEQ30, The Revised Mystical Experience Questionnaire; MGH-ATRQ Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire; MINI, Mini International Neuropsychiatric Interview; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self-rated; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SAE, serious adverse event; SDS, Sheehan Disability Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; UK, United Kingdom; VAS, visual analogue scale; WSAS, Work and Social Adjustment Scale; YMRS, Young Mania Rating Scale.

[1] On site clinic visits; visits allowed remotely will have the MADRS performed by telpehone and other assessments will be done electronically.

[2] If additional visits are needed to ensure adequate time for discontinuation of prior antidepressant therapy, visits should occur weekly prior to the psilocybin session (V3). At subsequent screening period visits (V1a, V1b, etc), medications taken and any changes in medications since the previous visit and C-SSRS will be obtained, in addition, to other assessments at the study clinician's discretion. Assessments may be performed over several days, but all scales should be completed on the same day.

[3] The "Baseline/Screening" version will be administered at Screening and the "Since Last Visit" version will be administered at all other visits.

[4] See Section 7.2.4 for complete list of required tests to be performed.

[5] All women.

[6] For women of child-bearing potential only.

[7] Site is to document method of contraception agreed to be used by each participant.
[8] To be administered immediately after the psilocybin session.
[9] **Blood pressure will be monitored before discharge.**

5D-ASC – The Five Dimension Altered States of Consciousness Questionnaire measures the acute drug effects.
EBI – The Emotional Breakthrough Inventory is an 8-item brief measure intended to index the degree to which an individual experiences his/her emotion during a psilocybin session. It is a VAS style scale, typically with units from 0 to 100. It is typically rated within 24 h of a psychedelic experience and ideally within 5 h of the 'end' of the psychedelic experience or once acute drug effects have significantly subsided.
HAM-D-17 – The 17-item Hamilton Depression Rating scale measure the degree of symptom severity in depressed patients.
GAD-7 – The Generalized Anxiety Disorder scale is a 7-item participant completed scale to assess anxiety in a participant.
MADRS – the Montgomery-Asberg Depression Scale is a clinician rated outcome measure to assess a participant's level of depression.
QIDS-SR-16 – Quick Inventory of Depressive Symptomatology scale is a participant-rated scale to assess their depression.
SDS – The Sheehan Disability Scale is a patient-reported outcome measure used to assess functional impairment and associated disability.
C-SSRS – Columbia-Suicide Severity Rating Scale assesses treatment-emergent suicidal thoughts. This scale should be administered prior to dosing if possible.
WSAS – Work and Social Adjustment Scale is a self-report scale used to assess psychosocial functioning and to predict durability of response to antidepressant treatment.

5 POPULATION

5.1 Number of Participants

A total of 12 participants are planned to be enrolled in the study.

5.2 Inclusion Criteria

Participants meeting all the following inclusion criteria at Screening (V1) should be considered for admission into the study.

1. Signed ICF.

2. 18 years of age or older at Screening (V1)**; less than age 65 at Screening**.

3. Must meet DSM-5 criteria for BP-II, depression episode based on medical records, clinical assessment and documented completion of the version 7.0.2 MINI.

4. HAM-D-17 (17-item) score ≥18 at Screening (V1) and at Baseline (V2). YMRS < 10 at V1 and V2.

5. Failure to respond to an adequate dose and duration of ≥ 2 or more pharmacological treatments for the current episode as determined through the MGH-ATRQ and the episode > 3 months and < 2 years. Failure includes inadequate response to an adequate duration and dose or failure to reach an adequate dose and duration due to lack of tolerance. Augmentation with an add on treatment counts as an additional treatment.

6. Have successfully discontinued all serotonergic medications at least 2 weeks prior to Baseline (V2) (see Section 8.5.3).

7. Ability to complete all protocol required assessment tools without any assistance or alteration to the copyrighted assessments, and to comply with all study visits.

5.3 Exclusion Criteria

Participants meeting any of the following exclusion criteria at Screening (V1) will not be enrolled in the study.

Psychiatric Exclusion Criteria:

1. Current or past history of bipolar I disorder, schizophrenia, psychotic disorder (unless substance induced or due to a medical condition), , delusional disorder, paranoid

personality disorder, schizoaffective disorder, or borderline personality disorder, as assessed by a structure clinical interview (version 7.0.2 MINI).

2. Current cognitive behavioral therapy (CBT) that will not remain stable for the duration of the study. CBT cannot be initiated within 21 days of baseline.

3. Current (or remission< 1 year) alcohol or drug abuse as defined by DSM-5 at Screening (V1).

4. Significant risk of suicide based on the C-SSRS prior to randomization defined as (a) a score of "3" or "4" on Questions 2 or 13; or (b) a score of "2" or higher on Questions 1a, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 14 over the past 13 months. Or, if active suicidal activity or ideation during the current episode, eligibility will be determined at the investigator's discretion.

5. Depression secondary to other medical conditions.

6. Other personal circumstances and behavior judged to be incompatible with establishment of rapport or safe exposure to psilocybin.

General Medical Exclusion Criteria:

8. Women who are pregnant, nursing, or planning a pregnancy. Participants who are sexually active must agree to use a highly effective contraceptive method (as listed in Section 8.5.2) throughout their participation in the study. Women of child bearing potential must have a negative urine pregnancy test at Screening (V1) and Baseline (V2).

9. Cardiovascular conditions: recent stroke (< 1 year from signing of ICF), recent myocardial infarction (< 1 year from signing of ICF), uncontrolled hypertension (blood pressure > 140/90 mmHg or QTc > 450 msec) or clinically significant arrhythmia within 1 year of signing the ICF.

10. Uncontrolled OR insulin-dependent diabetes.

11. Seizure disorder.

12. Positive urine drug screen for illegal drugs or drugs of abuse (to include but not limited to opiates, PCP, cocaine, amphetamines, methamphetamines, barbiturates and methadone; cannabis for medicinal purposes or recreational use is permitted) at V1 and V2**.** Any positive urine drug test will be reviewed with participants to determine the pattern of use and eligibility will be determined at the investigator's discretion in conjunction with thestudy physician.

13. Current enrollment in any investigational drug or device study or participation in such within 30 days of Screening (V1).

14. Current enrollment in an interventional study for depression or participation in such within 30 days of Screening (V1).

15. Abnormal and clinically significant results on the physical examination, vital signs, ECG, or laboratory tests at Screening (V1).

16. Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal or any other major concurrent illness that, in the opinion of the investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if he/she takes part in the study.

5.4 Participant Screening

Participants will be recruited from general practitioners and specialized psychiatric services. Those participants considered eligible for the study will be further assessed to confirm eligibility after the participant has signed an ICF. All participants will then be seen weekly for at least 3 weeks prior to the Psilocybin Session (V3) to ensure the safe discontinuation of current antidepressant therapy required by the protocol. Rescreening of participants considered not eligible for the study will be allowed.

5.5 Deviation from Inclusion/Exclusion Criteria

No deviations will be permitted from the Inclusion or Exclusion Criteria.

6 STUDY CONDUCT

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Section 4.3). A detailed description of each assessment may be found in Section 6.2.

6.1 General Instructions

Participants will be recruited from general practitioners and specialized psychiatric services. Those participants considered eligible for the study will be further assessed to confirm eligibility after the participant has signed an ICF.

6.2 Study Procedures by Time Point

6.2.1 Screening Period

The participant will be seen initially to evaluate suitability for the study. All participants will be seen at the clinic weekly for a minimum of 3 weeks prior to psilocybin administration (Psilocybin Session, V3) to ensure safe discontinuation of current antidepressant therapy required by the protocol, and to conduct psychoeducation.

At the initial Screening visit (V1), the following assessments will be performed and recorded. These assessments may be performed over several days, but all scales should be completed on the same day. All clinician or participant-rated assessments throughout the study will be captured electronically.

- ICF
- Medical history
- Prior and current medications; the participant will be tapered from prohibited medications (see Section 8.5.3), if any, under the supervision of the study clinician
- Review of inclusion/exclusion criteria (Section 5)
- MINI version 7.0.2
- HAM-D-17
- MGH-ATRQ
- YMRS
- C-SSRS (Last 13 Months)

- QIDS-SR-16
- Vital signs (ie, sitting blood pressure, pulse, body temperature, and respiratory rate)
- Weight
- 12-lead ECG
- Blood and urine samples for:
  - Clinical laboratory tests
  - Urinalysis
  - Urine drug screen
  - Urine pregnancy test for all women of childbearing potential
- Document contraceptive method to be used by the participant
- All participants will undergo an in-person preparatory session before receiving access to a digital study platform (Longboat) for psychoeducation.
- All participants will meet with study therapist to begin psychoeducation and preparation for their psilocybin experience.

At subsequent screening period visits (V1a, V1b, etc), medications taken and any changes in medications since the previous visit, and the C-SSRS will be obtained in addition to other assessments at the study clinician's discretion.

6.2.2 Baseline Visit – Visit 2 – Day -1

The Baseline visit (V2) should occur 3 to 6 weeks after initial Screening (V1) + < 7-day window. At the Baseline visit (V2), the participant's eligibility will be confirmed by reviewing the Inclusion/Exclusion Criteria (Sections 5.2 and 5.3) and updating the medical history. If the participant is out of the < 7-day window, all baseline assessments are to be repeated, except randomization. The Baseline visit (V2) should occur the day before the anticipated psilocybin session. The following procedures will be performed and recorded at the Baseline visit (V2):

- MADRS
- HAM-D-17
- YMRS
- C-SSRS (Since Last Visit)
- SDS
- GAD-7
- Q-LES-Q-SF
- QIDS-SR-16

- WSAS
- Vital signs (ie, sitting blood pressure, pulse, body temperature, and respiratory rate)
- Urine samples for:
  - Urine drug screen
  - Urine pregnancy test for all women of childbearing potential
- Medications taken and any changes in medications since the previous visit.
- Reviewing the Inclusion/Exclusion Criteria (Sections 5.2 and 5.3)

If the participant continues to meet the eligibility criteria, the therapist will review the psychoeducational material and the anticipated psilocybin session with the participant. If the participant remains eligible, the participant will receive 25mg psilocybin per study protocol the next day (V3).

6.2.3 Visit 3 – Day 0 – Psilocybin Session (25mg)

At the psilocybin session (the day of IP administration), the following are to be obtained:

- Vital signs (ie, sitting blood pressure, pulse, body temperature, and respiratory rate)
- Administer IP (Section 8.3). A full description of the activities of the psilocybin session is found in the Study Manual. After the acute effects of the psilocybin pass, participants will be discharged to go home with a chaperone.
- 5D-ASC
- YMRS
- C-SSRS (Since Last Visit)
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AEs and Serious AEs (SAEs) (Sections 9 and 10).

6.2.4 Visit 4 – Day 1 Postdosing

On the day following IP administration, the participant will return to the study site for a safety check and to discuss their experience during IP during the psilocybin administration session. The following will be obtained at this visit:

- MADRS
- YMRS
- C-SSRS (Since Last Visit)
- Emotional Breakthrough Inventory (EBI)
- QIDS-SR-16
- CEQ
- MEQ30
- Vital signs (ie, sitting blood pressure, pulse, body temperature, and respiratory rate)
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 9 and 10).

Participants will be reminded to remain off any antidepressant medications until after V7.

6.2.5 Visit 5 – 1 Week Postdosing

The participant will visit the clinic 1 week (7 days ± 1 day) following IP administration; they will meet with the study therapist and the following assessments will be obtained at this visit:

- MADRS
- YMRS
- C-SSRS (Since Last Visit)
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 9 and 10).

Participants will be reminded to remain off any antidepressant medications until after V7.

6.2.6 Visit 6 –Week 2 Postdosing

The participant will be contacted by telephone 2 weeks (14 days ± 1 day) following IP administration; the following assessments will be obtained at this visit:

- MADRS
- YMRS
- C-SSRS (Since Last Visit)
- SDS
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 9 and 10).

Participants will be reminded to remain off any antidepressant medications until after V7.

6.2.7 Visit 7 – Week 3 Postdosing

The participant will visit the clinic 3 weeks (21 days ± 1 day) following IP administration; they will meet with the study therapist and the following assessments will be obtained at this visit:

- MADRS
- YMRS
- C-SSRS (Since Last Visit)
- SDS
- GAD-7
- Q-LES-Q-SF

- QIDS-SR-16
- WSAS
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 9 and 10).

6.2.8 Visit 8 –6 Weeks Postdosing

The participant will visit the clinic 6 weeks (42 days ± 3 days) following IP administration. All clinician or participant-rated assessments throughout the study will be captured electronically:

- MADRS
- YMRS
- C-SSRS (Since Last Visit)
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 9 and 10).

6.2.9 Visit 9 – 9 Weeks Postdosing

The participant will be contacted by telephone 9 weeks (63 days ± 3 days) following IP administration; the following assessments will be obtained:

- Remote-rater MADRS
- YMRS
- C-SSRS (Since Last Visit)
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 9 and 10).

6.2.10 Visit 10 – 12 Weeks Postdosing End of Study

The participant will visit the clinic 12 weeks (84 days ± 3 days) following IP administration; they will have a termination meeting with the study therapist and the following assessments will be obtained:

- MADRS
- YMRS
- C-SSRS (Since Last Visit)
- SDS

- GAD-7
- Q-LES-Q-SF
- QIDS-SR-16
- WSAS
- Medications taken and any changes in medications since the previous visit
- AEs and SAEs (Sections 9 and 10).

6.3 Premature Discontinuation

If the participant's participation in the study is terminated prematurely for any reason, the reason for such Early Termination (ET) should be documented and the V110(EOS) procedures should be performed as noted in Section 6.2.11.

A termination electronic Case Report Form (CRF) page should be completed for every participant who is randomized, whether the participant completes the study or not. The reason for any ET should be indicated on this form; as much information should be provided as possible. The primary reason for a participant discontinuing early should be selected from the following standard categories of ET:

- *Screen Failure:* Participant does not qualify to participate in the study.
- *Lack of efficacy:* Participants who meet the following criteria after the psilocybin session will be evaluated by a study clinician, hospitalized if appropriate, and treated according to the national standard of care guidelines. They will be followed until the end of the study if informed consent is maintained:
  a. become suicidal as determined by clinical judgement and/or by C-SSRS as stated in the Exclusion Criteria
  b. showed scores of MADRS and/or QIDS-SR-16 increased by < 30% between the visits
  c. showed scores of MADRS and/or QIDS-SR-16 increased by < 30% for 3 consecutive visits
- *Adverse Event*: Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the participant, are grounds for discontinuation. This includes serious and nonserious AEs regardless of relation to the IP.
- *Death:* The participant died.
- *Withdrawal of Consent*: The participant or caregiver desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the participant gave a reason for withdrawing, it should be recorded in the CRF.
- *Protocol Violation*: The participant's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (eg, drug

noncompliance, failure to return for defined number of visits). The violation necessitated early discontinued from the study.

- *Lost to Follow-Up*: The participant stopped coming for visits and study personnel were unable to contact the participant.
- *Noncompliance:* The participant was noncompliant with study visits or procedures.
- *Other*: The participant was discontinued for a reason other than those listed above.

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7 DESCRIPTION OF STUDY PROCEDURES

7.1 Efficacy Assessments

7.1.1 Montgomery-Asberg Depression Rating Scale

MADRS evaluations will be performed at Baseline, Day 1, and Weeks 1, 2, 3, 6, 9, and 12 (V2, V4, V5, V6 V7, V8, V9, and V10, respectively). The MADRS is a clinician-rated scale measuring depression severity, consisting of 10 items, each scored from 0 (normal) to 6 (severe), for a total possible score of 60; higher scores denote greater severity.[24] The structure of the telephone-based interview will be controlled through the use of The Structured Interview Guide for the MADRS (SIGMA),[41] which provides structured probes to ensure standardisation of administration and comprehensive coverage of 10 questions.

7.1.2 Quick Inventory of Depressive Symptomatology

The 16-item QIDS-SR-16 a self-rated scale designed to assess the severity of depressive symptoms in the nine diagnostic symptom domains of a major depressive episodes, exclusive of atypical or melancholic symptoms.[29] The QIDS-SR-16 is sensitive to change with various treatments, demonstrating its utility in research settings. The total score ranges from 0 to 27 with 0 representing no depression and 27 representing severe depression. The total score is the sum of the 9 symptom domains. The QIDS-SR-16 will be collected at every clinic visit or contact with the participant.

7.1.3 Sheehan Disability Scale

The SDS is a brief, 5-item self-report inventory that assesses functional impairment in work/school, social life, and family life. The total score ranges from 0 to 30 with 0 representing no impairment and 30 representing severe impairment. The last two items of the scale (Days Lost and Days Unproductive) do not count toward the total score. Each domain is rated on a 10 -point visual analogue scale (VAS).[32] The SDS will be obtained at Baseline, and Weeks 3, 6 and 12 (V2, V7, and V10, respectively).

7.1.4 Generalized Anxiety Disorder scale

The GAD -7 is useful in primary care and mental health settings as a screening tool and symptom severity measure for the seven most common anxiety disorders.[34] Participants choose one of 4 severity scores associated problems related to the common anxiety disorders and then indicate the degree to which these problems caused functional and/or social difficulties. Scores are determined by calculating the values for each column. A total score is obtained by the sum of all total column values. The GAD-7 will be obtained at Baseline, and Weeks 3 and 12 (V2, V7, and V10, respectively).

7.1.5 Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a self-report measure designed to enable investigators to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. The summary scores were found to be reliable and valid measures of these dimensions in a group of depressed outpatients. The Q-LES-Q measures were related to, but not redundant with, measures of overall severity of illness or severity of depression within this sample. These findings suggest that the Q-LES-Q measures may be sensitive to important differences among depressed patients that are not detected by the measures usually employed. [13]

The Q-LES-Q-SF will be administered to the participant and will be obtained at Baseline, and Weeks 3 and 12 (V2, V7, and V10, respectively).

7.1.6 Work and Social Adjustment Scale

The WSAS is a 5-item self-report scale used to assess psychosocial functioning and to predict durability of response to antidepressant treatment.[21] Each of the 5 questions is rated on a scale from 0 to 8, where 0 is no impairment and 8 is very severe impairment. A WSAS score above 20 appears to suggest moderately severe or worse psychopathology.[25] Scores between 10 and 20 are associated with significant functional impairment but less severe clinical symptomatology. Scores below 10 appear to be associated with subclinical populations.

The WSAS will be performed at Baseline and Weeks 3 and 12 (V2, V7, and V10, respectively), and will be captured electronically.

7.2 Safety Assessments

7.2.1 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS[31] ; Oqendo, MA et al 2003) will be used to detect and measure the current intensity of the patients' specific attitudes, behaviors, and plans to attempt suicide. The C-SSRS will be included at the screening visit, the baseline visit, during all study visits, and in all scheduled follow up phone calls and at end of study for all subjects. Significant risk of suicide based on the C-SSRS defined as answering "YES" to question 4 or 5 for "Suicidal Ideation" [past 1 month] on the Columbia-Suicide Severity Rating Scale, and/or answering "YES" to any question for "Suicidal Behavior" [past 3 months] on the Columbia-Suicide Severity Rating Scale[33] .

7.2.2 Young Mania Rating Scale (YMRS)

The Young Mania Rating Scale is the most often used scale to assess the degree of manic symptoms a patient has (Young et al., 1978)[44]. This scale will be used to screen out patients in mixed or manic states at enrollment and will be used during the trial to assess if the psilocybin treatment may be inducing mania.

7.2.3 Vital Signs

Blood pressure (sitting for at least 3 min), respiratory rate, body temperature, and pulse rate will be obtained at Screening, Baseline, Day 0, and Day 1 (V1, V2, V3, and V4, respectively).

7.2.4 Electrocardiogram

Standard 12-lead ECGs will be obtained at Screening (V1).

7.2.5 Clinical Laboratory Tests

Blood samples will be obtained at Screening (V1), Day 1 for the following:

- *Hematology:* hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count (with differential), and platelet count.

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

Urine samples will be obtained at Screening (V1) and Baseline (V2) for the following:

- *Urinalysis:* A dipstick urinalysis will be performed for blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, and urobilinogen only at Screening (V1).

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

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

Laboratory samples will be analyzed locally.

In the event of an unexplained clinically significant abnormal laboratory test value, the test should be repeated and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

7.2.6 Adverse Events

All AEs occurring after the participant signs the ICF and up to the last study event will be recorded. Any AEs occurring before the start of treatment (ie, before the dose of the IP on Day 0 [V3]) will be recorded in the medical history. Any AE ongoing at V10 (EOS/ET) will be followed until resolution or no longer considered clinically significant by the investigator.

See Section 9 and 10 for additional information.

7.3 Other Assessment Instruments

7.3.1 Hamilton Depression Rating Scale – 17-item

The HAM -D-17 17-item scale is used to measure the degree of symptom severity in depressed patients.[16] The HAM-D -17 rating will be performed by the investigator using the eCOA device at the Screening (V1) and Baseline (V2) only. The total score from this assessment will be used as eligibility criteria prior to treatment (minimal total symptom score ≥18). The Structured Interview Guide for the HAM-D-17 (SIGH-D) will be administered.[40]

7.3.2 Mini International Neuropsychiatric Interview

The MINI was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-5 and International Classification of Diseases-10. Validation and reliability studies have been done comparing the MINI to the Structured Clinical Interview for DMS-5 Patient Edition and the Composite International Diagnostic Interview (a structured interview developed by the World Health Organization). Version 7.0.2 of the MINI will be used for this study. The results of these studies show that the MINI has similar reliability and validity properties, but can be administered in a much shorter period (mean 18.7 ± 11.6 min, median 15 min) than the above referenced instruments. It can be used by clinicians after a brief training session.[33]
At Screening (V1), participants will be assessed for BP-II, as documented by DSM -5 criteria, and the lack of other psychiatric diagnoses will be confirmed by use of the MINI.[33]

7.3.3 Massachusetts General Hospital-Antidepressant Treatment History Questionnaire

The MGH-ATRQ is a self-rated scale used to determine treatment resistance in major depressive disorder.[7] The scale examines the efficacy (improvement from 0%, not improved at all to 100% completely improved, and adequacy of a treatment. Participants are asked by clinician about treatment adherence to each medication trial and examines the participants' antidepressant history to identify pseudo-resistance and treatment resistance. The MGH-ATRQ will be collected at Screening (V1) only.

7.3.4 The Challenging Experience Questionnaire

Acute adverse psychological reactions to classic hallucinogens ("bad trips" or "challenging experiences"), while usually benign with proper screening, preparation, and support in controlled settings, remain a safety concern in uncontrolled settings (such as illicit use contexts). Anecdotal and case reports suggest potential adverse acute symptoms including affective (panic, depressed mood), cognitive (confusion, feelings of losing sanity), and somatic (nausea, heart palpitation) symptoms. Responses to items from several hallucinogen-sensitive questionnaires (Hallucinogen Rating Scale, the States of Consciousness Questionnaire, and the Five-Dimensional Altered States of Consciousness questionnaire) in an Internet survey of challenging experiences with the classic hallucinogen psilocybin were used to construct and validate a Challenging Experience Questionnaire. The stand-alone CEQ was then validated in a separate sample. Seven CEQ factors (grief, fear, death, insanity, isolation, physical distress, and paranoia) provide a phenomenological profile of challenging aspects of experiences with psilocybin. Factor scores were associated with difficulty, meaningfulness, spiritual significance, and change in well-being attributed to the challenging experiences. The factor structure did not differ based on gender or prior struggle with anxiety or depression. The CEQ provides a basis for future investigation of predictors and outcomes of challenging experiences with classic hallucinogens.[3] The CEQ will be administered the day after the psilocybin session on day 1 (V4) and 2 weeks after the psilocybin session on day 14 (V6).

7.3.5 The Revised Mystical Experience Questionnaire

The 30-item revised Mystical Experience Questionnaire (MEQ30) was previously developed within an online survey of mystical-type experiences occasioned by psilocybin-containing mushrooms. The rated experiences occurred on average eight years before completion of the questionnaire. The current paper validates the MEQ30 using data from experimental studies with controlled doses of psilocybin. Data were pooled and analyzed from five laboratory experiments in which participants (n=184) received a moderate to high oral dose of psilocybin (at least 20 mg/70 kg). Results of confirmatory factor analysis demonstrate the reliability and internal validity of the MEQ30. Structural equation models demonstrate the external and convergent validity of the MEQ30 by showing that latent variable scores on the MEQ30 positively predict persisting change in attitudes, behavior, and well-being attributed to experiences with psilocybin while controlling for the contribution of the participant-rated intensity of drug effects. These findings support the use of the MEQ30 as an efficient measure of individual mystical experiences. A method to score a "complete mystical experience" that was used in previous versions of the mystical experience questionnaire is validated in the MEQ30, and a stand-alone version of the MEQ30 is provided for use in future research.[2] The MEQ30 will be administered the day after the psilocybin session on day 1 (V4) and 2 weeks after the psilocybin session on day 14 (V6).

7.3.6 Five Dimension Altered States of Consciousness Questionnaire

The 5D-ASC measures the acute drug effects using 5 primary dimensions and respective subdimensions to assess alterations in mood, perception, and experience of self in relation to environment and thought disorder. The 5 dimensions include *oceanic boundlessness*, *anxious ego dissolution*, *visionary restructuralization*, *auditory alterations*, and *reduction of vigilance*.[9,10,35] This will be administered immediately after the psilocybin session on Day 0 (V3).

7.3.7 Emotional Breakthrough Inventory

The EBI is a VAS that describes the intensity and quality of the emotional experience following the psilocybin session, developed by the Imperial College London. This is collected on Day 1 (V4) electronically.

7.4 Protocol Deviations

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock, and deviations considered having a serious impact on the efficacy results will be reported in the scientific publication resulting from this study.

Protocol deviations will be summarized by center and grouped into different categories, as follows:

- those who entered the study even though they did not satisfy the entry criteria;
- those who developed withdrawal criteria during the study but were not withdrawn;
- those who received the wrong treatment or incorrect dose;
- those who took any prohibited medications during the study.

8 INVESTIGATIONAL PRODUCT (IP) MANAGEMENT

8.1 Description

Information about the IP is provided in Table 8.1.

Table 8.1 Details of Investigational Product

	Psilocybin
Ingredient	Psilocybin
Manufacturer	Juniper Pharma Services Ltd, 8 Orchard Place, Nottingham Business Park, Nottingham, NG8 6PX, UK
Dose	25 mg
Route	Oral
Formulation	Capsule
Strength(s)	5 mg

8.1.1 Formulation

Matching psilocybin capsules, 5 mg, are manufactured by Juniper Pharma Services, Ltd.

8.1.2 Storage

No pharmacy involvement is planned. All IP will be kept in a medication room under a triple lock system.There will be limited access to the IP: only the PI, Sub-I(s) and study coordinators will have acess to the IP. The Sub-I (s) will be licensed psychiatrists credentialed through the Sheppard Pratt Physicians PA (SPPPA).

The high-density polyethylene (HDPE) bottles of IP are to be stored as indicated in the Study Manual. Deviations of storage temperature outside this required range should be documented. Bottle of IP should not be frozen. If any component of the IP is damaged, the site PI must be notified as soon as possible to request replacement.

8.2 Packaging

Psilocybin capsules are packaged into HDPE containers with child-resistant, tamper-evident screw cap lids with a mounted desiccant by Fisher Clinical Services UK Ltd (Langhurstwood Road, Horsham, West Sussex, RH12 4QD, UK). Labeling of the IP will also be done by Fisher. Each bottle contains 5 capsules for a single dose administration. Labels are affixed on to the bottles consistent with regulations in participating countries. Single individual bottles will be provided for use by a given participant.

8.3 Dose and Administration – see below

8.3.1 Goals

The psychotherapeutic goals of the psilocybin session are to:

- Ensure psychological safety essential for optimal clinical efficacy
- Allow participant's subjective experience to unfold naturally within the boundaries of the therapeutic intention set at the preparation

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- Maintain participant 's attention and awareness on the experience of the present moment thus allowing exposure and processing of the challenging emotional states and memories
- Generation of insights and solutions for the resolution of challenging personal situations, conflicts and traumatic experiences

8.3.2 Methods

Psychotherapeutic methods of the psilocybin session have the following objectives:

- Psychological safety: effective management of anxiety is essential to safety, tolerability and efficacy of psilocybin.
- It has also been shown in previous studies that severe prolonged anxiety in the beginning of the experience could adversely affect the efficacy of psilocybin, therefore the management of anxiety during the onset of the session is an essential skill of psilocybin therapists. Anxiety during the onset of action is not uncommon, and the therapists are specially trained to recognize and actively manage participants through such periods of anxiety until the subject is comfortable enough to continue on their own. Planning two dose sessions with the first at a lower dose has been found helpful. The examples of such active guiding may include saying:
    - *Remember you enrolled in the study of psilocybin for treatment of your depression. As psilocybin takes effect, some anxiety and fear are expected. It is part of the process. Remember we practice relaxation and breathing experiences for situations like this?*
    - *Let's take deep breaths together and focus on the sensations of the breath throughout the body. As you do this, pay attention to the rhythm of your breath and watch it becoming deeper and slower. Let go of muscle tension with every exhalation.*

  Therapists are asked to validate the feeling of anxiety without providing interpretations of perceptual disturbances or guiding participants towards a particular image or memory, other than encouraging them to stay relaxed and open to the emergent experiences.

  In the modern research setting, any anxiety during the onset of psilocybin action responded well to reassurance and meditation.

- Self-directed Enquiry and Experiential Processing

  In preparation for the psilocybin session, therapists demonstrate and practice skills of self-directed inquiry and experiential processing with participants. Participants are encouraged to face and explore their experience, including the challenging ones. During the peak and later stages of the session, self-directed inquiry and experiential processing become essential for participants to develop a different perspective on their personal challenges and conflicts, and to generate their own solutions. Such self-generated insights are not only therapeutic because of the emotional resolution, but also empowering to participants. This approach is used in MDMA-assisted psychotherapy for treatment of PTSD and is particularly helpful in the event of emergent traumatic memories.

8.3.3 Structure of the Psilocybin Session

In preparation for dosing on Day 0 (V3), after it is confirmed at Baseline (V2) the participant remains eligible to participate in the study they will receive:

- Dosing session 25-mg treatment bottle: 5 × 5-mg capsules

The psilocybin session is supported by two trained mental health clinicians at least one at a doctoral level (the other may be at a masters level) or similar degrees of experience such as an M.D., psychiatrist. Additionally, the study psychiatrist will be in the immediate vicinity of the session to respond to any emergencies.

On the day of the session, participants come in early in the morning with the goal to take the IP around 9 am.

Prior to dose administration, a team of psychotherapists will review the rules and structure of the session with the participant again. Once all the questions are answered, and the participant reconfirms their consent for the session, they will be administered the IP (5 capsules) with a full glass of water. Delaying the intake of IP may induce unnecessary anxiety in participants, therefore it is recommended to have the treatment room prepared for the start of the session before participant’s arrival.

The treatment rooms in all trial sites are furnished in soft furniture in muted colors to create a non-clinical calming feel. All treatment rooms are equipped with a high-resolution sound system that allows for simultaneous ambient and earphone listening. The playlist is designed jointly with experts from Johns Hopkins University and the Imperial College London to provide nonverbal guidance. This is the same playlist being used in the Compass Pathways FDA-approved Phase II-b study.

Participants will then be encouraged to lie down, practice relaxation and breathing exercises, and listen to calming music. Therapists might want to revisit the intention for the treatment session with the participant and again, ask the question *"What would it look and feel like to be free of depression?"* Such revisions immediately prior to the session provide an implicit direction for the subjective experience during the psilocybin session.

Once the effects of psilocybin become noticeable, participants are encouraged to put on eyeshades and earphones and focus on their internal experience.

Psychotherapists will sit on both sides of the patient's couch. Psychotherapists are discouraged from reading, using laptops or phones, eating or drinking other than water during the first 2-3 hours of the session.

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

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

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

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

At the end of the session and after the effects of IP are no longer evident, participants become more talkative and interactive. The role of the therapists now is to ensure that experiential processing is complete with some emotional resolution. In those cases where there is still anxiety or despair at the end of the session, participants are encouraged to relax and reflect for a longer period of time. The provisions are made for therapists to stay with the participant until the effects of the drug have fully subsided, and participant is assessed to be comfortable and fully sober. This is assessed through engaging in 'small talk' about non-contentious topics unrelated to the content of the session. The therapist might for example ask:

- *It is almost 6 o'clock. What do you normally do at this time of the day?*
- *What do you usually have for dinner?*
- *What do you like to cook?*

Participants and therapists are discouraged to discuss the content of the session until the next day to avoid premature consolidation of the insights.

At the end of the session, therapists and participants might have a light meal together to mark the closure of the session. Participant's family or friends might also be invited to join the meal if participant consents.

After the safety assessments, participants will be discharged in the care of a family member or a friend. Please refer to the section of safety for more detailed information on discharge assessments and unexpected adverse events.

8.3.4 Before the Session

On the day of the psilocybin session, the participant arrives at the clinical center between 8AM and 9AM. It is essential for the therapist and the supportive assistant (the therapeutic team) to prepare the room and take care of all the logistics prior to the participant's arrival.

The therapist and assistant should welcome the participant shortly following his/her arrival and allow for the expression of any questions or concerns. Since participants are likely to be at least mildly anxious, it is important to validate their anxiety and assure them it is common to be anxious prior to a new experience. The time following arrival and prior to entering the treatment room should be as minimal as possible, as "waiting outside" (even if reading a book) tends to increase anxiety.

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

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

Key components of mental set/intention are also reviewed:

- Every experience is welcome; nothing to censor or avoid.

- Face anything that looks potentially frightening as rapidly and openly as possible.
- Reach out for grounding, support or sharing at any time.
- Remember key instructions: Trust, Let Go, Be Open.
- Remember to breathe deeply if needed.
- You'll never be left alone.
- No need to entertain the therapist/assistant.
- This is your day. We're with you, whether you need us or not.

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

Before the drug's effects begin, it is helpful to re-establish the participant's stated goals for the treatment and to revisit the question: "What does feeling better or recovery feel like?" The participant is reminded that their primary task during this session is to simply collect new and interesting experiences which can then be discussed with the therapist during the integration phase. The therapist can remind the participant of the purpose of the psilocybin therapy and the role of experiential processing, namely allowing the participant to be open and curious to whatever arises and encountering thoughts and feelings previously unknown to them. It should be emphasized that this process inherently requires letting go and a willing passivity to the psychedelic experience; the willingness to let go is correlated with better outcomes in psilocybin therapy.[6] The therapist should remind the participant that the therapeutic team will be supporting them at all times.

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

8.3.5 Onset of Action

8.3.5.1 Setting and Music

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

8.3.5.2 Managing Anxiety

Transient anxiety is often reported as participants encounter changing psychological content. Such anxiety might be viewed as natural and even necessary. It can manifest in different ways, ranging from mild intractability and avoidance of the emerging experiences to extreme paranoia. In most cases, anxiety resolves on its own accord and can be minimized with skillful interpersonal support. Psilocybin provides a unique opportunity for a participant to normalize anxiety and view it as excitement and experience the encounter with honest ambivalence.

During the acute onset of action, the participant might experience perceptual changes in visual, auditory or olfactory modes, and a range of unusual physical sensations. These experiences could be anxiety-provoking, particularly in psychedelically naïve participants. During preparation, the therapist encourages the participant to become curious about these experiences and to freely explore them. If the participant continues to manifest anxiety and emotional distress, the therapist may offer therapeutic touch or interpersonal grounding, if that is something the participant has agreed to during preparation and has been rehearsed.

“I want to state again my commitment to be here for you. I will do whatever is necessary to make this a safe place for you so that you can fully experience whatever comes up. If what comes up is difficult, I’d like you to try and stay with it and explore it as much as you can. Please ask me for whatever you need.”

If the participant is agitated and/or frightened, simple reminders could be helpful:

"You remember that you are participating in a clinical trial of a new medication for your depression. During preparation, we talked about possible anxiety, unusual sensations and intense emotions. This is simply the drug taking effect. It is safe; you will not be harmed. These challenging experiences pass by very quickly if you relax and just watch them. You will return to everyday reality as the effect of psilocybin wanes."

The therapist encourages the participant to focus inwards and fully immerse him/herself in all aspects of the experience. The participant may want to practice guided imagery or breathing relaxation techniques in preparation. Please see the scripts for guided imagery, breathing exercise and 'raisin meditation' in the study manual.

8.3.5.3 Managing Distractions and Avoidance

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

Participant: *"Yeah, everything has this shiny quality to it, like it's made of this otherworldly metal."*

Therapist: *"I wonder if you could stay with that otherworldly experience and see where it takes you."*

And if the participant continues to engage in the conversation, the therapist can say:

Therapist: *"Perhaps you can focus attention to the details so that we can talk about it later. If you talk about this now, you will be less able to focus on the experience and might miss important details."*

Here the therapist again acknowledges the participant's comment without introducing new topics. Then the therapist guides the participant back to his/her present experience.

Sometimes a participant might ask to go to the bathroom or have a drink of water. The sudden and urgent character of such requests might suggest that they are really trying to avoid emerging material. In such cases, the therapist might suggest:

"We will take a bathroom break at the end of this piece of music."

"I will get you water in a little while. Why don't you put the eye shades back on and relax for a few minutes?"

If a participant is trying to avoid a difficult experience, they might listen to the suggestion and relax.

8.3.5.4 Challenging Shifts versus Adverse Events

Emotions and feelings can shift quickly during psilocybin experiences. Such shifts must be differentiated from distress that requires active guidance. It is essential that the therapist use his/her clinical judgment to establish whether the participant is in need of the therapist's quiet and non-intrusive presence, or active guidance. During preparation, the participant has been informed that they can ask for support from the therapist for any reason at any time, especially when they do not feel able to navigate through a particular experiential sequence.

Support can be in the form of therapeutic touch, verbal reassurance, guided imagery or a breathing exercise. It is advisable to apply one technique at a time to allow for minimal intervention and interference with the participant's unique process. In the preparatory session, the therapist and participant may have discussed the most helpful ways to support in case of emotional distress. It might be useful to remind the participant about this conversation:

"You remember I told you that anxiety is to be expected and we have agreed that I may support you though physical grounding. If you feel anxious, please reach out for my hand or let me know what else might help you."

Or:

Participant: "The negative feelings are getting really overwhelming now"

Therapist: "Do you remember the conversation we had about negative experiences?"

Participant: "Yeah. You suggested I should sit with them."

Therapist: "How does that sound to you?"

Participant: "It's going to be difficult, but I'll try. If I can't, can you help me?"

Therapist: "Yes I'll do all I can to help you. I'd like you to tune out and just stay focused on what you're feeling right now."

Participant: "Okay, I'm doing that. It doesn't feel good."

Therapist: "As you focus on it, are you feeling it altering or changing in any way?"

Participant: "It feels like it's coming and going."

Therapist: "How do you feel about that?"

Participant: "It's difficult."

Therapist: "What's making it difficult?"

Participant: "I'm not sure."

Therapist: "Would it be helpful if I held your arm?"

Participant: "Yes, I think that would help."

As soon as the participant is comfortable, the therapist should encourage him/her to return to further exploration. Remind the participant that you will be there if needed and that there will be a chance during integration to talk through the experience.

Therapists may talk with clinicians/therapists and may coordinate psychotherapy outside the trial. Information should be provided regarding the integration of the psilocybin session with any psychotherapy the participant is currently receiving (and will continue to receive throughout the duration of the study and cannot have been initiated within 21 days of baseline).

8.3.6 Emergency Protocol

The general principle is that if the participant cannot be calmed down through all the available methods, and is presenting a current threat to him/herself or others, the first choice of medical treatment is oral benzodiazepines. The participant should be made safe in the least invasive and distressing way possible. Note, however, that in research with psilocybin in different university settings over almost two decades, there has never been a need for rescue medications. The psychiatrist will be available to speak with the participant and provide further assessment. A decision will be made by the study clinician with the subject a week before dosing as to whether to have a patient supplied benzodiazepine emergency dose available at the time of dosing.

8.3.7 Peak Experience

With adequate dosage and an acute onset of action, a 'peak' experience may occur about 60-90 minutes after ingestion. Factors that influence the quality and intensity

of peak experiences include the participant's ability to stay with whatever arises in awareness, their ability to relax and let go of expectations and fears, , etc.

Non-dual experiences have been shown to positively correlate with the magnitude and durability of the clinical response, so this state needs to be attended with care. The goal of the therapist is to encourage and support the participant in being fully present and relaxed in this state. Verbal communication should be minimal.

Participants who reach peak experience tend to be quiet; even non-responsive. In the unlikely event that a participant would express a need to prematurely attempt to share such an experience, it should be viewed as distraction or avoidance. The therapist needs to encourage the participant to stay quiet and focus on the sensations, insights and feelings, and to collect as many details about the experience as possible so as to be able to relate the story later. However, in true ego-loss and non-dual experiences, there is no ego present. When recalled in memory, participants usually claim such states to be beyond language.

Transcendent non-dual experiences are frequentThere may be perceptions that extend well beyond the usual sense of self, such as feelings of oneness in which the participant experiences an openness and enhanced connection to their own humanity and to the surrounding environment. Such experiences can be difficult to interpret and may challenge a therapist's own worldview. The therapist is not required to understand, support or even have an opinion about the nature or content of these experiences, but it is essential that they validate them and convey openness toward the participant's own view of them without dismissing or pathologizing any experience based on its unusual content. These experiences may provide the participant with a perspective that goes beyond identification with their personal narrative.

It is equally important that a therapist not show disappointment when a participant does not report a profound transcendental experience. The therapist should remain mindful of his/her own reactions and responses to the participant's experiences and validate any and all of them. However, that doesn't mean that the therapist must agree with unusual, magical thinking. Validation of the experiences simply means acknowledging the courage of opening up to the experience and the possibility that any experience will serve the intention of the session.

8.3.8 Conclusion of the Psilocybin Session

The drug effects last for 4-6 hours. During the final phase, it's important that the participant doesn't prematurely terminate the session by excessive talking. Even if little appears to be happening, periodic returns to the couch with music, headphones and eyeshade often provide for not only unexpected new experiential content, but safe and complete closure. The use of music is continued and light conversations between the therapist and participant are encouraged. This serves the dual role of

re-orienting the participant to everyday reality and enabling the therapist to assess for immediate risks. By having a light casual conversation about dinner or the weather, the therapist assesses whether the participant is struggling to re-enter reality, or is distressed by the content of the session.

This can be discussed over a light meal with the participant, which—if they choose—can include the participant's family members. The therapist needs to be mindful that the participant is adequately reoriented to everyday reality, and be certain that the participant is fully competent to travel before making the journey home. If the participant requires a longer period of time to return to normality, the therapist is expected to remain with the participant. If the participant requires emotional support due to a difficult session, the therapist is required to support the participant until the discomfort is resolved and the participant is fully back in everyday reality. The therapist should use open questions and empathic attention, as in previous sessions, to ensure that the participant feels supported.

8.3.9 Specific Criteria for Discharge from the Facility on the Day of Drug Administration

Participants will remain in the treatment facility for a full 8 hours after the start of the session, to ensure that the psilocybin effects have fully subsided. Participants are then assessed for safety by the therapists and the study clinician. Blood pressure will be monitored before discharge.

Participants are observed in the facility to ensure that they are fully ambulatory, have good balance, are psychologically stable, and can perform activities of daily living. Participants are also asked to complete the QIDS-SR-16 (Quick Inventory of Depressive Symptomatology – Self-Rated), C-SSRS (Columbia-Suicide Severity Rating Scale) and 5D-ASC (5 Dimensions of Altered States of Consciousness). These scales will be performed by the study team and will allow the clinician to assess participant 's emotional and cognitive stability, risk for suicidality and whether the perception-altering effects of psilocybin have subsided.

When judged safe and functional, participants are discharged in the care of a friend or a family member who will stay with the participant overnight. Plans for the follow-up visit the next morning are confirmed prior to discharge.

When the participant is ready to leave, he/she will be given information regarding the time and location of the next session (safety assessment and integration within 24 hours of the psilocybin session) as well as contact numbers if help is needed before then. The therapist is expected to be available 9am-5pm on weekdays and the hospital's 24/7 number can be used on weekends and evenings to contact the study team. The participant must agree not to drive or use alcohol during the evening following the psilocybin

session. The therapist should check in with the participant and family member(s) later in the evening to confirm that the participant is comfortable and safe.

8.3.10 Planning for Unexpected Adverse Events

For participants who may have an unusually prolonged experience or remain in severe distress and are considered at risk for adverse reactions a psychiatrist will assess and arrange appropriate care.

In over 2,000 research sessions with psilocybin, there has never been a need for emergency interventions.

8.4 Accountability

The investigator must keep an accurate accounting of the number of IP units delivered to the site and administered to participants during and at the completion of the study, as per FDA and DEA standards of Schedule I drug management. This should be done on an IP accountability log in the regulatory binder. The IP must be administered to participants only by an appropriately qualified person. The IP is to be used in accordance with the protocol by participants who are under the direct supervision of the investigator. Investigators should maintain records that document adequately that the participants were administered the IP dose specified by the protocol and reconcile all IPs received at the site before final disposition. A chain of custody should be used to keep record of IP transportation from the storage room to the treatment room and back as well as of person conducting the study drug administration.

Unused or expired study drug will be returned to Fisher Clinical Services, Inc., for destruction at the study conclusion

8.5 Concomitant Therapy

All prescription and non-prescription medications (eg, over-the-counter drugs and herbal supplements) that participants report taking during the 30 days prior to Screening (V1) will be assessed and recorded at that visit. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use.

Concomitant medication refers to all drugs and therapies used from the time the ICF was signed through the end of study participation.

Changes, additions, or discontinuations to medications will be assessed and recorded in the clinical form during each study visit.

8.5.1 Permissible Medications

Medications for the management of concurrent anxiety and insomnia, or nonpsychiatric medications that have a potential psychotropic effect are permitted within the following limitations. From the initial Screen Visit (V1) through final study visit (V10, EOS), participants are permitted adjunctive use of benzodiazepines (up to 2 mg of lorazepam equivalents per day for insomnia and anxiety if it is not taken within 12 h before the psilocybin dose. Prescription and nonprescription medications with psychoactive properties that are used as needed for nonpsychiatric conditions (eg, pseudoephedrine for allergies or cold symptoms) should be used no more than 2 times a week and not in the 12 hours before any study assessment. Documentation of the use of adjunctive anxiolytics, hypnotics, or medication with potential psychotropic properties (including over-the-counter preparations) will be obtained at each clinic visit.

Therapy considered necessary for the participant's welfare may be given at the discretion of the study clinician.

8.5.2 Definition of Women of Childbearing Potential and/or Acceptable Contraceptive Methods

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently steriled (i.e. has had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy).

A woman who is not of childbearing potential is considered to be postmenopausal after at least 12 months without menstruation. The following methods of contraception, if used properly and used for the duration of the study, are generally considered highly effective:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal

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

Periodic abstinence (ie, calendar, symptothermal, or postovulation methods, and tubal ligation/occlusion) are not an acceptable form of contraception for this study.

These methods of contraception also apply to partners of male participants.

The investigator and each participant will determine the appropriate method of contraception for the participant during the participation in the study. This will be documented at Screening (V1).

If a participant or the partner of a male participant becomes pregnant during the study, the investigator will notify the FDA immediately after the pregnancy is confirmed according to Section 12.5.

8.5.3 Prohibited Medications

Participants are to be discontinued from serotonergic medications at least 2 weeks prior to Baseline (V2). Serotonergic medications include but are not limited to the selective-serotonin reuptake inhibitors, selective-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, antipsychotics, and/or lithium. Common medications in these classes are noted below but the list is not exhaustive. These medications are not to be reintroduced to the participant until after V8 (Week 3). Participants who require concomitant medication(s) specifically for the treatment of depression at any time through the duration of the study will be assessed for reasons of resuming their medications and followed until 12 weeks post psilocybin administration. The study clinician should initiate treatment of symptoms of depression based on the clinical investigator's judgement and may change the venue of therapy (ie, outpatient to inpatient) if deemed clinically necessary. The intervention may be a combination of somatic (eg, approved antidepressant medication) and nonsomatic (various forms psychotherapy, eg, CBT) whose therapeutic intention is remediation of the depressive episode. Because the anticipated half-life of psilocybin is approximately 3 hours, and only 2 administrations of test

product is permitted, no known issues regarding PK or pharmacodynamic interactions are envisioned within approximately 7 days of product administration.

8.5.3.1 Selective-Serotonin Reuptake Inhibitors

- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

8.5.3.2 Selective-Norepinephrine Reuptake Inhibitors

- Desvenlafaxine
- Duloxetine
- Levomilnacipran
- Milnacipran
- Venlafaxine

8.5.3.3 Tricyclic Antidepressants

- Amitriptyline
- Amoxapine
- Clomipramine
- Desipramine
- Doxepine
- Imipramine
- Maprotiline
- Nortriptyline
- Protriptyline
- Trimipramine

8.5.3.4 Monoamine Oxidase Inhibitors

- Phenelzine
- Segeline
- Tranylcypromine

8.5.3.5 Antipsychotics

- Aripiprazole
- Asenapine
- Clozapine
- Lurasidone
- Olanzapine

- Quetiapine
- Risperidone
- Ziprasidone

8.5.3.6 Other Prohibited Medications

- Efavirenz
- Lorcaserin
- Serotonin-acting dietary supplements (such as 5-hydroxytryptophan or St. John's wort)

8.5.4 Rescue Medication

Rescue medications may be used during and after the psilocybin session.

The decision to medicate a participant will depend on responsible physician judgement that they are capable of maintaining the safety of the patient and others without medical intervention.

- Benzodiazepine anxiolytics is the pharmacological intervention of choice in case of acute psychological distress (eg, medications such as lorazepam or alprazolam that have a rapid onset, a short time until peak plasma concentration, and a short duration of therapeutic action; these medications will be given via the oral route.

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

Information of how to manage subjects during difficult psychological states are detailed in the Study Manual (see attached).

8.6 Compliance

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

9 ADVERSE EVENTS

Throughout the course of the study, all AEs will be monitored and recorded on an AE CRF, including the AE's description, start and end date, seriousness, severity, action taken, and relationship to the IP. If AEs occur, the first concern will be the safety of the study participants.

Per ICH E2A: An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

The investigator will promptly notify the local IRB of all SAEs and nonserious AEs occurring during the clinical trial so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the product under clinical investigation are met.

The investigators have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

9.1 Documenting Adverse Events

AEs occurring from when the participant signs the ICF until the last study event will be recorded. Any AEs occurring before the start of treatment (ie, before the dose of the IP on Day 0 [V3]) will be recorded in the medical history. Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period. Investigators should document all significant illnesses that the participant has experienced within 3 months of the Screening visit. Additional illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the CRF.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal clinical laboratory test results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to IP

discontinuation, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

At each time point, the investigator will determine whether any AEs have occurred by evaluating the participant. AEs may be directly observed, reported spontaneously by the participant or by questioning the participant at each time point. Participants should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine intensity, causality and seriousness, in accordance with the definitions in Sections 9.2, 9.3, and 10.1, respectively. The investigator's assessment must be clearly documented in the study site's source documentation with the investigator's signature.

The investigator should report all AEs on the AE page(s) of the CRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (eg, "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Sections 9.2 and 9.3.

9.2 Assessment of Intensity

Each AE will be classified according to the following criteria:

Mild:	The AE does not interfere in a significant manner with the participant's normal level of functioning.
Moderate:	The AE produces some impairment of functioning, but is not hazardous to the participant's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the participant's health.

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on participant/event outcome at the time of the event.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over several days, those changes should be recorded separately (with distinct onset dates).

9.3 Assessment of Causality

Each AE will be assessed as to its relationship to the IP, based on the following criteria. Although the attribution by the investigator will be collected for reported events, for analytic purposes a temporal association with the use of the IP will be assumed sufficient for at least plausible association.

Not related:	No causal relationship exists between the IP and the AE, but an obvious alternative cause exists, eg, the participant's underlying medical condition or concomitant therapy.
Possibly related:	A connection with the administration of the IP appears unlikely, but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IP; (2) it could not readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant; or (3) it follows a known pattern of response to the IP.
Related:	There is a reasonable/plausible possibility that the AE may have been caused by the IP.

When assessing the relationship to the IP, the following criteria will be considered:

- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

9.4 Other Action Taken for Event

1 = None (ie, no treatment was required)

2 = Medication required (ie, prescription and/or OTC medication was required to treat the AE)

3 = Hospitalization or prolongation of hospitalization required (ie, hospitalization was required or prolonged because of the AE, whether medication was required)

4 = Other

9.5 Adverse Event Outcome

1 = Recovered/Resolved (ie, the participant fully recovered from the AE with no residual effect observed)

2 = Recovering/Resolving (ie, the AE improved but has not fully resolved)

3 = Not Recovered/Not Resolved (ie, the AE itself is still present and observable)

4 = Recovered/Resolved with Sequelae (ie, the residual effects of the AE are still present and observable, including sequelae/residual effects)

5 = Fatal (ie, 'fatal' should be used when death is a direct outcome of the AE)

6 = Unknown

9.6 Clinical Laboratory Changes

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the clinical report form:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of IP
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

Combined elevations of aminotransferases and bilirubin, either serious or nonserious, and whether causally related, meeting the criteria of a potential Hy's Law case (total bilirubin level ≥2 × upper limit of normal [ULN] with simultaneous ALT or AST ≥3 × ULN) should always be reported to the sponsor as soon as possible following the procedures outlined in Section 10.2 for SAE reporting, with the investigator's assessment of seriousness, causality, and a detailed narrative.

9.7 Overdose

Any instance of overdose (suspected or confirmed) must be communicated to the local IRB within 24 h and be fully documented as an AE or SAE if it meets the SAE criteria. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

9.9 Adverse Event Follow-up

All AEs will be followed until resolved or stable and the outcome documented on the CRF.

10 SERIOUS ADVERSE EVENTS

10.1 Definition of Serious Adverse Event

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a participant who received psilocybin.
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE 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 events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
  - Development of drug dependency or drug abuse

Definition of Terms

Life threatening: An AE is life threatening if the participant was at immediate risk of death from the event as it occurred; ie, it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AEs (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the

physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to IP should also be reported and managed as an SAE.

The investigator should follow participants with AEs until the event has resolved or the condition has stabilised. In case of unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.

10.2 Reporting Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 10.1). If the AE is considered serious, the investigator should report this event to the IRB according to its standard operating procedures.

If the investigator detects an SAE in a study participant after the last scheduled follow-up visit, and considers the SAE related or possibly related to this study's IP administration, the investigator should report it to IRB of the other site.

All information about SAEs will be collected and reported via the local IRB SAE form and sentto IRBNet . The investigator should send the initial report within 24 h of becoming aware of the SAE.

If the SAE has not resolved at the time the investigator submits an initial SAE report, the investigator must provide a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing). The investigator should not delay reporting an SAE in order to obtain additional information.

All SAEs shall be followed until resolution, until the condition stabilizes, or until the participant is lost to follow-up, or otherwise explained. Once the SAE is resolved, the corresponding AE CRF page shall be updated. Additionally, any relevant laboratory test reports, consultation reports from other health care professionals, discharge summaries, or other information that has been gathered about the event shall be transmitted to the sponsor.

The original SAE form should be kept at the study site.

11 STATISTICS

11.1 Statistical Methods

The Safety Population will consist of all randomized participants who receive study treatment, regardless of whether or not treated. This population will be used for all summaries of participant accountability, demographic and baseline data, and safety information, including AE incidence.

The Full Analysis Set (FAS) will consist of all participants randomized who also receive the dose of IP.

The modified intention-to-treat population will consist of all participants in the FAS that have at least 1 post dose assessment.

The Per Protocol (PP) population will consist of all participants in the FAS who do not have a major protocol deviation. Major protocol deviations will be reviewed and determined prior to unblinding. The PP population will be used for supportive sensitivity analyses.

11.2.1 Efficacy and Outcome Measures

- MADRS
- QIDS-SR-16
- SDS
- GAD-7
- Q-LES-Q-SF
- WSAS

11.2.2 Analysis of Efficacy

The primary efficacy endpoint (change from Baseline in MADRS total score at Week 3) will be evaluated with a mixed effects model for repeated measures analysis. The model will include treatment, visit, study site, prior psychedelic experience, treatment by visit interaction, participant as a random effect, and baseline MADRS total score. A sensitivity analysis will be performed on the primary MMRM model adding treatment by study site or country interaction into the model. This exploratory analysis will be performed for information only due to the small sample size and lack of comparison ranges.

The 3 secondary efficacy endpoints that are dichotomous variables (proportion of participants who are responders, remitters, and sustained responders) will be analyzed using the Cochran Mantel Haenszel chi square test. A stepdown procedure to correct for multiplicity will be employed.

Time to event measures will be evaluated using Kaplan-Meier methods.

Response and remission rates will be summarized at each visit.

Change from baseline in continuous efficacy measures, including the QIDS-SR-16 scale and GAD-7 total scores at each point, will be analyzed based on last observation carried forward data using an analysis of covariance model, with treatment and study

site as factors, and the respective baseline score as the covariate. The exploratory analyses for quality of life and wellbeing, functioning and associated disability, cognitive function, and anxiety are not hierarchical; there will be no correction for multiplicity in these analyses.

Scores for all efficacy endpoints, including the Q-LES-Q-SF and the EQ VAS, will be summarized over time using descriptive statistics for all visits during the observation period.

The covariate selection process will be addressed in the SAP to be approved before any analyses are undertaken.

11.2.3 Analysis of Safety

Safety analyses will be performed using data from the Safety Population. Safety will be evaluated based of AEs, vital signs, clinical laboratory assessments, and ECG findings.

11.2.3.1 Columbia-Suicide Severity Rating Scale

Item scores from the C-SSRS, all visits by randomized treatment, the item scores from the version assessing suicidality since the last visit, and all postbaseline visits (V3 to V10, inclusive) by treatment will be tabulated. Summary statistics of suicidal ideation and suicidal behavior following IP administration will be presented by randomized treatment.

11.2.3.2 Adverse Events

AEs will be coded by Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) classification. All reported AEs with onset or worsening after the administration of study medication will be included in the analysis. The incidence of AEs will be summarized by treatment group, and by severity and relationship to IP. Serious AEs and AEs leading to withdrawal from the study will be tabulated.

A TEAE is defined as any AE that has an onset on or after the dose of IP, or any pre-existing condition that has worsened on or after the dose of IP.

The incidence of TEAEs and treatment-related AEs will also be summarized by maximum severity and most-related relationship to IP by MedDRA primary system organ class and PT. The summary will include the total number and percentage of participants reporting an event. In counting the number of events reported, a continuous event, ie, reported more than once and which did not cease, will be counted only once; non-continuous AEs reported several times by the same participant will be counted as multiple events.

11.2.3.3 Vital Signs

Changes from Baseline in vital signs, blood pressure (systolic and diastolic), body temperature, pulse rate, and respiratory rate, will be summarized for each treatment group using descriptive statistics. The last measurement obtained prior to IP administration will serve as baseline. The percentage of participants with values outside clinically important limits will be summarized. A listing of weight at V1 will be provided.

11.2.4 Demographic and Baseline Characteristics

Treatment groups will be compared with respect to participant demographics and baseline characteristics will be summarized using descriptive statistics, no formal statistical analysis tests will be performed.

11.2.5 Data Safety Monitoring Board

The DSMB will consist of three clinicians experienced with mood disorders. Of the three, one will have experience with psychedelics. The DSMB will meet every six months. All SAEs will be reported and to the SP IRB

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

The study will be performed in accordance with this protocol, US investigational new drug (IND) regulations (21 Code of Federal Regulations [CFR] 312), ICH guidelines for Good Clinical Practice (GCP), and the regulations on electronic records and electronic signature (21 CFR 11).

The study will also be performed in accordance with U.S. laws and regulations where the research is carried out.

12.2 Steering Committee

A Steering Committee will not be used for this study.

12.3 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/ IEC. Approval is required for the study protocol, protocol amendments, ICFs, participant information sheets, and advertising materials. No IP will be shipped to a site until written IRB/IEC authorization has been received by the sponsor or its representative.

12.4 Informed Consent

Participants should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH guidelines. The principal investigator or a designated representative will provide the sponsor or its representative with a copy of the IRB/IEC-approved ICF before the start of the study.

12.5 Exposure in Utero During Clinical Studies

The FDA must be notified of any participant who becomes pregnant within 30 days of receiving the IP. Reporting after the follow-up visit or ET is done voluntarily by the investigator.

The FDA must be notified of any male participant whose partner becomes pregnant within 30 days of the participant receiving the IP. Reporting after any follow-up visit or ET is done voluntarily by the investigator.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a participant, or the partner of a male participant, using the CRF pregnancy within 24 h of becoming aware of the event. The investigator should make every effort to follow the

participant until completion of the pregnancy with complete pregnancy outcome information, including normal delivery and/or induced abortion. The adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted foetus), the investigator should follow the procedures for reporting SAEs outlined in Section 10.

For reports of pregnancy in the partner of a male participant, the SAE form (if associated with an adverse outcome) should be completed with the participant's randomization number, initials, and date of birth, and details regarding the partner of the male participant should be entered in the narrative section.

12.6 Records Management

The investigator grants permission to personnel and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, paper and electronic, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

12.7 Source Documentation

Note that a variety of original documents, data, and records will be considered as source documents in this trial.

12.8 Study Files and Record Retention

The investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

13 STUDY DISCONTINUATION

The Principal Investigator reserve the right to terminate the study at the investigator's site at any time. The Principal Investigator will inform the IRB/IEC of the termination. In terminating the study, the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and sensitive, and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is obtained. However, authorized regulatory officials, IRB personnel, and its authorized representatives are allowed full access to the records.

Identification of participants and CRFs shall be by study number only. All identifying information including initials, screening and treatment numbers. If required, the participant's full name may be made known to an authorized regulatory agency or other authorized official as required by law.

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