THE SAFETY AND EFFICACY OF PSILOCYBIN AS AN ADJUNCTIVE THERAPY IN PARTICIPANTS WITH TREATMENT-RESISTANT DEPRESSION

DRUG:	Psilocybin 3-[2-(Dimethylamino)ethyl]-1*H*-indol-4-yl dihydrogen phosphate
STUDY NUMBER:	COMP003
CLINICAL PHASE:	2
EudraCT NUMBER:	2018-002577-22
SPONSOR:	COMPASS Pathways, Ltd 20 Old Bailey London, England, EC4M 7AN, UK
VERSION NUMBER:	V1.0
VERSION DATE:	11 Sep 2019

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: The safety and efficacy of psilocybin as an adjunctive therapy in participants with treatment-resistant depression

Study No: COMP003

Protocol Version No: V1.0

Protocol Version Date: 11 Sep 2019

This study protocol was reviewed and approved by the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practices (GCP) as described in the Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Sponsor Approval:

Signature: _____ Date: 11-SEP-2019

Name (print): Hans Eriksson, MD PhD MBA

Title: Chief Medical Officer
COMPASS Pathways, Ltd

STUDY NUMBER COMP003

THE SAFETY AND EFFICACY OF PSILOCYBIN AS AN ADJUNCTIVE THERAPY IN PARTICIPANTS WITH TREATMENT-RESISTANT DEPRESSION

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to psilocybin are the confidential and proprietary information of COMPASS Pathways, Ltd (COMPASS), and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of COMPASS.

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Code of Federal Regulations (CFR) for Good Clinical Practices (GCP) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by COMPASS or specified designees. I will discuss the material with them to ensure that they are fully informed about psilocybin and the study.

Principal Investigator Name (printed)	Signature
Date	Site Number

STUDY SUMMARY

Title:	The Safety and Efficacy of Psilocybin as an Adjunctive Therapy in Participants with Treatment-Resistant Depression
EudraCT Number:	2018-002577-22
Clinical Phase:	2
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 explore effectiveness of 25 mg of psilocybin as an adjunctive therapy in participants with TRD.
Target Population:	TRD
Number of Participants:	Approximately 20 participants with simultaneous study drug administration to up to six participants
Objectives:	The main purpose of this study is to investigate the efficacy of 25 mg psilocybin adjunct to serotonergic antidepressants in TRD participants via the following objectives. **Primary Objective** The primary objective of this study is to explore the efficacy of 25 mg psilocybin as an adjunct therapy to antidepressants in improving depressive symptoms. **Secondary Objectives** The secondary objective is to evaluate the safety and tolerability of psilocybin in participants with TRD based on adverse events (AEs), changes in vital signs, electrocardiograms (ECGs), clinical laboratory tests and suicidal ideation/behavior (measured using the Columbia-Suicide Severity Rating Scale [C-SSRS]) score. **Exploratory Objective** The exploratory objectives are to evaluate the effects of psilocybin on quality of life, wellbeing and anxiety.
Study Design:	This is a Phase IIb, international multicenter, fixed-dose, open-label study. The study population will include adult men and women, 18 years of age or older, with TRD. Participants with TRD are defined as those who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single or recurrent episode of major depressive disorder (MDD) without psychotic features which have failed to respond to an adequate dose and duration of 2, 3 or 4 pharmacological treatments for the current episode; the duration of the current episode must be at least 3 months but not more than 2 years. Participants will be outpatients and will be recruited primarily through referrals from general practitioners and specialised psychiatric services. After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric

Interview, Version 7.0.2 (MINI 7.0.2), the Hamilton Depression Rating Scale (17-item; HAM-D-17), the Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire (MGH-ATRQ), the C-SSRS, and McLean Screening Instrument for Borderline Personality Disorder. At the initial Screening visit (V1), the participant will also be evaluated with the Quick Inventory of Depressive Symptomatology – Self Rated - 16 item (QIDS-SR-16). Additionally, a medical history, an ECG, blood tests, and vital signs will be obtained.

Once a participant completes all Screening (V1) assessments and all screening data is entered into the Electronic Data Capture (EDC), the Medical Monitor (MM) and Clinical Assessment Technologies Team (CAT) will review data entered and issue approval, if the participant is eligible.

The participant will meet with a therapist for a minimum of 3 visits during screening. These are safety sessions and will cover what to expect during the psilocybin session. The therapist and the participant will review psychoeducational materials provided at the time of enrolment.

All participants will be evaluated for safety at the clinic weekly for a minimum of 3 weeks prior to psilocybin administration. 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.

At Baseline [V2, Day -1], the participants will undergo a baseline assessment that will consist of the HAM-D-17, Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression – Severity scale (CGI-S) and Improvement scale (CGI-I), QIDS-SR-16, C-SSRS, Generalised Anxiety Disorder Scale 7-item Scale (GAD-7), Euro QoL-5 dimension-3 level (EQ-5D-3L; administered to both participant and caregiver [the latter is not mandatory]), Medication Adherence Report Scale – 5 item (MARS-5), vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential). After baseline data is entered into EDC, the CAT team will complete a final review to ensure the participant's continued eligibility. Participants cannot be progressed to V3 until this approval is received.

The psilocybin administration session (V3, Day 0) will last approximately 6 h and will be supported by a trained therapist. The study drug will be administered simultaneously to up to six participants. Blood pressure will be monitored continuously during the session. The psilocybin session may be video recorded for training and adherence monitoring. A full description of the activities of the psilocybin administration session is found in the Therapist Manual. After the acute effects of the psilocybin pass, participants will be evaluated for safety and accompanied home. On Day 1 (V4), the day following psilocybin administration, participants will be seen in person for a safety check, assessment of suicidality and clinical and self-report assessments, and to discuss their experience during the psilocybin session. 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.

Twenty participants will receive one dose of 25 mg psilocybin.

Participants will be seen at the clinic for Screening (V1 plus a minimum of 3 safety visits), Baseline (V2, Day -1), Day 0 (V3, Dosing), Day 1 (V4), Week 1 (V5), Week 2 (V6) and Week 3 (V7). Adverse events, serious adverse events (SAEs) and concomitant medication and therapies will be recorded at all clinic visits. The MADRS will be done by telephone and the other assessments will be done electronically.

Eligibility Criteria:

Inclusion Criteria

1. Signed ICF.
2. 18 years of age or older, depending on country-specific limits, at Screening (V1).
3. At least moderate MDD (single or recurrent episode as informed by DSM-5; duration of ≥ 3 months and ≤ 2 years) based on medical records, clinical assessment and documented completion of the version 7.0.2 MINI.
4. Hamilton Depression Rating Scale (17-item) score ≥18 at Screening (V1) and Baseline (V2, Day-1).
5. Currently receiving treatment with a selective serotonin reuptake inhibitor (SSRI; fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram or escitalopram) at, or above, a minimum locally approved therapeutic dose for at least 6 weeks before Screening (V1) and Baseline (V2, Day -1). Dose changes within the adequate range are acceptable. To be defined as an adequate study, adherence of at least 75% is needed based on participant estimate of percentage of doses that were taken.
6. Failure to respond to an adequate dose and duration of 2, 3, or 4 pharmacological treatments for the current episode as determined through the MGH-ATRQ and using the supplementary advice on additional antidepressants not included in MGH-ATRQ. Augmentation with an add on treatment counts as a second treatment, provided it is approved for the adjunctive treatment of MDD in that country.
7. McLean Screening Instrument for Borderline Personality Disorder <7 at Screening (V1).
8. Ability to complete all protocol required assessment tools without any assistance or alteration to the copyrighted assessments, and to comply with all study visits.

Exclusion Criteria

Psychiatric Exclusion Criteria:

1. Current or past history of schizophrenia, psychotic disorder (unless substance induced or due to a medical condition), bipolar disorder, delusional disorder, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder, as assessed by medical history, McLean Screening Instrument for Borderline Personality Disorder and a structured clinical interview (version 7.0.2 MINI).
2. Prior electroconvulsive therapy and/or ketamine for current episode.

3. Ongoing use of an antidepressant medication, including augmentation or combination therapies, other than a single SSRI at Screening (V1) and Baseline (V2, Day -1). Discontinuation from antidepressant medications, other than the ongoing SSRI, must have been completed 2 weeks prior to Baseline visit (V2, Day -1).
4. Current psychological therapies that will not remain stable within 21 days of the psilocybin session. Psychological therapies cannot be initiated within 21 days of baseline.
5. Current (within the last year) alcohol or substance use disorder as informed by DSM-5 (diagnosed by MINI 7.0.2) at Screening (V1).
6. Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, at Screening or at Baseline, or; (2) suicidal behaviors within the past year, or; (3) clinical assessment of significant suicidal risk during participant interview.
7. Depression secondary to other severe medical conditions according to clinicians' judgement.
8. Other personal circumstances and behaviour judged to be incompatible with establishment of rapport or safe exposure to psilocybin, including exposure to psilocybin within the past year and use of psychedelics, such as ayahuasca, during the current depressive episode.

General Medical Exclusion Criteria:

9. Women who are pregnant, nursing or planning a pregnancy. Male and female participants who are sexually active must agree to use a highly effective contraceptive method throughout their participation in the study. Women of child bearing potential must have a negative urine pregnancy test at Screening (V1) and Baseline (V2, Day -1).
10. Cardiovascular conditions: recent stroke (<1 year from signing of ICF), recent myocardial infarction (<1 year from signing of ICF), hypertension (blood pressure >140/90 mmHg) or clinically significant arrhythmia within 1 year of signing the ICF.
11. Uncontrolled or insulin-dependent diabetes.
12. Seizure disorder.
13. Positive urine drug screen for illicit drugs or drugs of abuse at Screening (V1) and Baseline (V2, Day -1). 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 the medical monitor (MM).
14. Current enrolment in any investigational drug or device study or participation in such within 30 days prior to Screening (V1).
15. Current enrolment in another clinical study of an investigational medical or participation in such within 30 days of Screening (V1).
16. Abnormal and clinically significant results on the physical examination, vital signs, ECG or laboratory tests at Screening (V1).

17. 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: Single 5-capsule oral psilocybin dose of 25 mg.

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

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 administration
- The proportion of participants with remission (defined as a MADRS total score ≤ 10) at Week 3 post psilocybin administration
- Changes from Baseline in CGI-S score at Week 3 post psilocybin administration.
- Incidence of AEs
- Change from Baseline to Day 1 in ECGs, and incidence of clinically important changes
- Change from Baseline to Day 1 and to Week 3 in clinical laboratory tests, and incidence of clinically important changes
- Change from Baseline to Day 1 in vital signs
- Incidence of changes from Baseline in the C-SSRS at each post-Baseline visit

Exploratory Endpoints:

- Change from Baseline to Week 3 in total scores of:
  - Participant EQ-5D-3L
  - Caregiver EQ-5D-3L (this assessment is not mandatory)
  - GAD-7
  - QIDS-SR-16
  - CGI-I
  - MARS-5 adherence to SSRI
- Change from Baseline to Day 1 in Positive and Negative Affect Schedule (PANAS)
- Summary of Five Dimension Altered States of Conscniousness questionnaire (5D-ASC) on the day of the psilocybin session (Day 0)

Efficacy Assessments:

- MADRS
- CGI-S
- CGI-I
- EQ-5D-3L (participant and caregiver, the latter is not mandatory)
- GAD-7

- QIDS-SR-16
- PANAS
- 5D-ASC
- C-SSRS

Safety Assessments:

- ECG
- Vital signs
- Clinical laboratory tests including liver function tests
- Suicide risk as assessed by the C-SSRS
- AEs and Serious AEs

Statistical Procedures:

Analysis Sets

The Safety Population will consist of all enrolled participants, 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 enrolled participants who receive the dose of investigational product (IP).

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

Efficacy Analyses

Since this is a single treatment open-label study, no statistical testing will be performed. The FAS and the PP populations will both be used for each secondary endpoint, if the two sets are not identical. For each of the secondary endpoints (MADRS, CGI-S, C-SSRS), measuring change from Baseline to Week 3, summary statistics will be provided.

Analysis of exploratory endpoints will be detailed in the Statistical Analysis Plan (SAP).

Safety Analyses

Safety data will be presented for the Safety Population. Safety will be evaluated based on AEs, ECGs, clinical laboratory tests, vital signs and suicidal ideation/behavior (measured using C-SSRS).

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
ATC	Anatomical Therapeutic Chemical
CAT	Clinical Assessment Technologies Team
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity scale
CI	confidence interval
COMPASS	COMPASS Pathways, Ltd
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EIU	Exposure In Utero
EOS	End of Study
EQ-5D-3L	Euro QoL-5 dimension-3 level
EQ VAS	Euro QoL visual analog scale
ET	early termination
FAS	Full Analysis Set
GAD-7	Generalised Anxiety Disorder 7-item Scale
GCP	Good Clinical Practice
h	hours
HAM-D-17	Hamilton Depression Rating Scale (17-item)
HDPE	high-density polyethylene
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation	Definition
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
MADRS	Montgomery-Asberg Depression Rating Scale
MARS-5	Medication Adherence Report Scale – 5 item
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire
min	minute
MINI 7.0.2	Mini International Neuropsychiatric Interview, Version 7.0.2
MM	Medical Monitor
MSI-BPD	McLean Screening Instrument for Borderline Personality Disorder
OTC	over-the-counter
PANAS	Positive and Negative Affect Schedule
PP	per protocol (analysis population)
PT	preferred term
QIDS-SR-16	Quick Inventory of Depressive Symptomatology – Self-Rated - 16 item
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression
ULN	upper limit of normal
VAS	visual analog scale
Worldwide	Worldwide Clinical Trials, Inc.

1 INTRODUCTION AND RATIONALE

The following is a summary of the information found in the current Investigator's Brochure (IB).[7]

1.1 Background

Psilocybin belongs to a class of drugs referred to as psychedelics (meaning 'mind-manifesting'). Specifically, psilocybin is considered a 5-hydroxytryptaminergic (serotonergic) psychedelic, along with other tryptamines such as dimethyltryptamine (DMT), ergolines such as lysergic acid diethylamide (LSD), and phenethylamines such as mescaline. Psilocybin was first isolated from psilocybe mushrooms by Hofmann in 1957, and later synthesised by him in 1958.[22] 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 US in 1970, and until the 1980s in Germany.[22,23] 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,[4,10,16] 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 (six men and six women) with moderate-to-severe, unipolar, treatment-resistant major depression (ISRCTN 14426797).[3] Each patient received two 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 Quick Inventory of Depressive Symptomatology – Self Rated - 16 item (QIDS-SR-16); QIDS-SR-16 scores were obtained from Week 1 to 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-SR-16 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%).

This study provides further support for the safety and efficacy of psilocybin for treatment-resistant depression (TRD) and motivates further studies to better examine the therapeutic potential of this approach. In this study, the aim is to explore effectiveness of 25 mg of psilocybin as an adjunctive therapy in participants with TRD. In addition, there is one ongoing study, COMP001, examining the safety and efficacy of psilocybin in participants with TRD and one study which has completed the in-clinic phase, COMP002, looking at the effects of psilocybin on cognitive and emotional function in healthy participants.

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).[14] Orally ingested psilocybin is metabolised (dephosphorylated) in the liver, and primarily transformed into the active hydroxy metabolite, psilocin. Psilocybin is detectable in plasma 30 min after administration [14,17,20,22] 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.[20] Psilocin's half-life ranges between 2 and 3 h, and is detectable 6 h after oral administration.[14,20] Hasler et al.[14] and Lindenblatt et al. [20] 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.[15] 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.[15]

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.[31] Reviews of the pharmacology of psilocybin is provided by Passie, and more current knowledge and perspective by Tylš et al.[22,30]

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.[24] 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.,[24] 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 1960s, 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).[7] These effects are both expected, and may be a necessary component of therapeutic response. Investigators must follow regulatory guidance under 21 Code of Federal Regulations (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.

1.2.4 Potential Risk to Foetal Development

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

1.2.5 Dosing Regimen

Carhart-Harris successfully evaluated two 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.[3] 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.[11]

This study will evaluate 1 psilocybin dose (25 mg psilocybin) under supportive conditions.

2 STUDY OBJECTIVES

The main purpose of this study is to investigate the efficacy of 25 mg psilocybin adjunct to serotonergic antidepressants in TRD participants via the following objectives.

2.1 Primary

The primary objective of this study is to explore the efficacy of 25 mg psilocybin as an adjunct therapy to antidepressants in improving depressive symptoms.

2.2 Secondary

The secondary objective is to evaluate the safety and tolerability of psilocybin in participants with TRD based on AEs, changes in vital signs, electrocardiograms (ECGs), clinical laboratory tests and suicidal ideation/behavior (measured using the Columbia-Suicide Severity Rating Scale [C-SSRS]) score.

2.3 Exploratory

The exploratory objectives are to evaluate the effects of psilocybin on quality of life, wellbeing and anxiety.

3 STUDY ENDPOINTS

3.1 Primary

The primary endpoint is the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from Baseline (Day -1) to 3 weeks post psilocybin administration.

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 3 post psilocybin administration
- The proportion of participants with remission (defined as a MADRS total score ≤ 10) at Week 3 post psilocybin administration
- Changes from Baseline Clinical Global Impression – Severity scale (CGI-S) at Week 3 post psilocybin administration
- Incidence of AEs
- Change from Baseline to Day 1 in ECGs, and incidence of clinically important changes
- Change from Baseline to Day 1 and to Week 3 in clinical laboratory tests, and incidence of clinically important changes
- Change from Baseline to Day 1 in vital signs
- Incidence of changes from Baseline in the C-SSRS at each post-Baseline visit

3.3 Exploratory

The exploratory endpoints are:

- Change from Baseline to Week 3 in total scores of:
  - Participant Euro QoL-5 dimension-3 level (EQ-5D-3L)
  - Caregiver EQ-5D-3L (this assessment is not mandatory)
  - Generalised Anxiety Disorder 7-item Scale (GAD-7)
  - QIDS-SR-16
  - Clinical Global Impression – Improvement scale (CGI-I)

- Medication Adherence Report Scale – 5 item (MARS-5) adherence to selective serotonin reuptake inhibitor (SSRI)

- Change from Baseline to Day 1 in Positive and Negative Affect Schedule (PANAS)

- Summary of Five Dimension Altered States of Conscniousness questionnaire (5D-ASC) on the day of the psilocybin session (Day 0)

3.4 Efficacy and Outcome Measures

Measures of interest include:

- MADRS

- CGI-S

- CGI-I

- EQ-5D-3L (participant and caregiver [latter is not mandatory])

- GAD-7

- QIDS-SR-16

- PANAS

- 5D-ASC

- C-SSRS

4 STUDY PLAN

4.1 Study Design

This is a Phase IIb, international multicenter, fixed-dose, open-label study. The study population will include adult men and women, 18 years of age or older, with TRD. Participants with TRD are defined as those who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single or recurrent episode of major depressive disorder (MDD) without psychotic features which have failed to respond to an adequate dose and duration of 2, 3, or 4 pharmacological treatments for the current episode; the duration of the current episode must be at least 3 months but not more than 2 years.

Participants will be outpatients and will be recruited primarily through referrals from general practitioners and specialised psychiatric services.

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI 7.0.2), the Hamilton Depression Rating Scale (17-item; HAM-D-17), the Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire (MGH-ATRQ), the C-SSRS, and McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). At the initial Screening visit (V1), the participant will also be evaluated with the QIDS-SR-16. Additionally, a medical history, an ECG, blood tests, and vital signs will be obtained.

Once a participant completes all Screening (V1) assessments and all screening data is entered into the Electronic Data Capture (EDC), the Medical Monitor (MM) and Clinical Assessment Technologies Team (CAT) will review data entered and issue approval, if the participant is eligible.

All participants will be evaluated for safety at the clinic weekly for a minimum of 3 weeks prior to psilocybin administration. 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 participant will meet with a therapist for a minimum of 3 visits during screening. These are called safety sessions and will cover what to expect during the psilocybin session. The therapist and the participant will review psychoeducational materials provided at the time of enrolment.

The day before the psilocybin session (≥ 24 h after Screening [V1]; V2, Day -1), the participants will undergo a baseline assessment that will consist of the HAM-D-17, MADRS, CGI-S, QIDS-SR-16, C-SSRS, GAD-7, EQ-5D-3L (administered to both participant and caregiver [the latter is not mandatory]), MARS-5, vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential).

After baseline data is entered into EDC, the CAT team will complete a final review to ensure the participant's continued eligibility. Participants cannot be progressed to V3 until this approval is received.

The psilocybin administration session (V3, Day 0) will last approximately 6 h and will be under trained therapist supervision and support. The study drug will be administered simultaneously to up to six participants. Blood pressure will be monitored continuously during the session. The psilocybin session may be video recorded for training and adherence monitoring. A full description of the activities of the psilocybin administration session is found in the Therapist Manual. After the acute effects of the psilocybin pass, participants will be evaluated for safety and accompanied home. 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. 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.

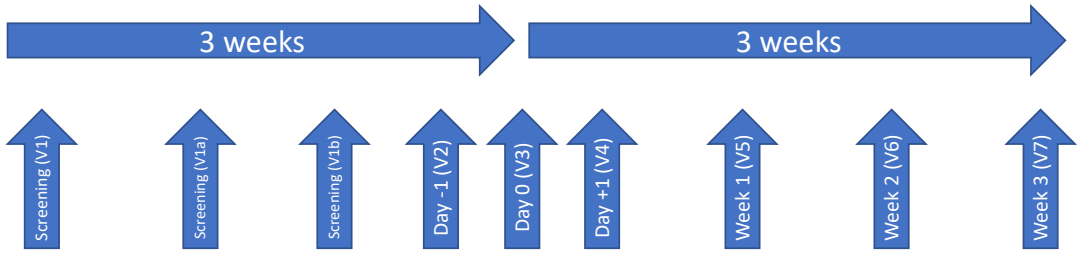
Twenty participants will receive one dose of 25 mg psilocybin.

Participants will be seen at the clinic for Screening (V1, plus a minimum of 3 safety visits), Baseline (V2, Day -1), Day 0 (V3, Dosing), Day 1 (V4), Week 1 (V5), Week 2 (V6) and Week 3 (V7). Adverse events, serious adverse events (SAEs) and concomitant medication will be recorded at all clinic visits. The MADRS will be done by telephone and the other assessments will be done electronically.

Clinicians are advised to continue the prescription of the participant's baseline SSRI (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram or escitalopram) for the duration of the follow-up period, ideally at the same dose.

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 Baseline			Time Post Psilocybin Session			
	Screening[1]	Screening Period	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21 (EOS/ET)
Visit	**1**	**1a, 1b**	**2**	**3**	**4**	**5**	**6**	**7**
Allowable Window	**-**	**Weekly**	**+ < 7 days**	**none**	**None**	**±1 day**	**±1 day**	**± 1 day**
Clinical Assessments and Procedures								
Informed consent	✓							
Medical history	✓		✓					
Inclusion/Exclusion Criteria	✓		✓					
MINI 7.0.2	✓							
HAM-D-17	✓		✓					
MGH-ATRQ	✓							
C-SSRS[2]	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓		✓	✓	✓			
Physical examination, including weight and height	✓							
12-Lead ECG	✓				✓			
Clinical laboratory tests[3]	✓				✓			✓
Urinalysis[3]	✓		✓		✓			
Urine drug screen[3]	✓		✓					
Urine pregnancy test[4]	✓		✓					

		3 weeks prior to Baseline			Time Post Psilocybin Session			
	Screening[1]	Screening Period	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21 (EOS/ET)
Visit	**1**	**1a, 1b**	**2**	**3**	**4**	**5**	**6**	**7**
Allowable Window	**-**	**Weekly**	**+ < 7 days**	**none**	**None**	**±1 day**	**±1 day**	**± 1 day**
Clinical Assessments and Procedures								
Documentation of contraceptive method to be used[5]	✓							
CGI-I					✓	✓	✓	✓
CGI-S			✓		✓	✓	✓	✓
MARS-5			✓			✓	✓	✓
Psilocybin dose				✓				
Prior/Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓
AE/SAEs	✓	✓	✓	✓	✓	✓	✓	✓
Participant Completed Assessments								
MSI-BPD	✓							
QIDS-SR-16	✓		✓	✓	✓	✓	✓	✓
EQ-5D-3L			✓			✓	✓	✓
GAD-7			✓		✓	✓	✓	✓
PANAS			✓		✓			
5D-ASC				✓[6]				
Remote-rater Assessment								
MADRS[7]			✓		✓	✓	✓	✓

Abbreviations: 5D-ASC = Five Dimension Altered States of Consciousness; AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; EQ-5D-3L = Euro QoL-5 dimension-3 level; ET = early termination; GAD-7 = Generalised Anxiety Disorder 7-item Scale; HAM-D-17 = Hamilton Depression Rating Scale (17-item); MINI 7.0.2 = Mini International Neuropsychiatric Interview, Version 7.0.2; MADRS = Montgomery-Asberg

Depression Scale; MARS-5 = Medication Adherence Report scale – 5 item; MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder; PANAS = Positive and Negative Affect Schedule; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology – Self Rated - 16 item; SAE = serious adverse event.

1 Screening (V1) will be performed 3 weeks prior to the Baseline visit (V2, Day -1).
2 The "Last 12 months" version will be administered at Screening and the "Since Last Visit" version will be administered at all other visits.
3 See Section 7.2.4 for complete list of required tests to be performed.
4 For women of child-bearing potential only.
5 For females of childbearing potential and all males; site is to document method of contraception agreed to be used by each participant.
6 To be administered immediately after the psilocybin session.
7 On site clinic visits; visits allowed remotely will have the MADRS performed by telpehone and other assessments will be done electronically.

Instruments (all measures below will be captured electronically):
5D-ASC – The Five Dimension Altered States of Consciousness questionnaire measures the acute drug effects.
C-SSRS - Columbia-Suicide Severity Rating Scale. This scale should be administered prior to dosing if possible.
EQ-5D-3L – The 3-level Euro QoL (EQ)-5D version (EQ‑5D‑3L) was introduced by the EuroQoL Group in 1990. The EQ-5D-3L essentially consists of two pages: the EQ-5D-3L descriptive system and the EQ visual analogue scale (EQ VAS).
HAM-D-17 – The 17-item Hamilton Depression Rating Scale measure the degree of symptom severity in depressed patients.
GAD-7 – The Generalised Anxiety Disorder Scale is a 7-item participant completed scale to assess anxiety in a participant.
MSI-BPD – The McLean Screening Instrument for Borderline Personality Disorder is a self-reporting screening tool to determine the presence of DSM-5 borderline personality disorder.
PANAS - Positive and Negative Affect Schedule measures the acute emotional drug effects.
QIDS-SR-16 – Quick Inventory of Depressive Symptomatology – Self Rated - 16 item is a participant-rated scale to assess their depression.
MARS-5 – Medication Adherence Report Scale – 5 item, self-report scale measuring adherence to the patients ongoing SSRI antidepressant
CGI-S – Clinical Global Impression – Severity scale, a clinician-rated measure of depression severity
CGI-I – Clinical Global Impression – Improvement scale, a clinician-rated measure of improvement

5 POPULATION

5.1 Number of Participants

A total of 20 participants with simultaneous study drug administration to up to 6 participants.

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, depending on country-specific limits, at Screening (V1).
3. At least moderate MDD (single or recurrent episode as informed by DSM-5; duration of ≥ 3 months and ≤ 2 years) based on medical records, clinical assessment and documented completion of the version 7.0.2 MINI.
4. Hamilton Depression Rating Scale (17-item) score ≥18 at Screening (V1) and Baseline (V2, Day -1).
5. Currently receiving treatment with a SSRI (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram or escitalopram) at, or above, a minimum locally approved therapeutic dose for at least 6 weeks before Screening (V1) and Baseline (V2, Day -1). Dose changes within the adequate range are acceptable. To be defined as an adequate study, adherence of at least 75% is needed based on participant estimate of percentage of doses that were taken.
6. Failure to respond to an adequate dose and duration of 2, 3, or 4 pharmacological treatments for the current episode as determined through the MGH-ATRQ and using the supplementary advice on additional antidepressants not included in MGH-ATRQ (Appendix III). Augmentation with an add on treatment counts as a second treatment, provided it is approved for the adjunctive treatment of MDD in that country.
7. McLean Screening Instrument for Borderline Personality Disorder <7 at Screening (V1).
8. 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 schizophrenia, psychotic disorder (unless substance induced or due to a medical condition), bipolar disorder, delusional disorder, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder, as assessed by medical history, MSI-BPD and a structured clinical interview (version 7.0.2 MINI).
2. Prior electroconvulsive therapy and/or ketamine for current episode.
3. Ongoing use of an antidepressant medication, including augmentation or combination therapies, other than a single SSRI at Screening (V1) and Baseline (V2, Day -1). Discontinuation from antidepressant medications, other than the ongoing SSRI, must have been completed 2 weeks prior to Baseline visit (V2, Day -1).
4. Current psychological therapies that will not remain stable within 21 days of the psilocybin session. Psychological therapies cannot be initiated within 21 days of baseline.
5. Current (within the last year) alcohol or substance use disorder as informed by DSM-5 (diagnosed by MINI 7.0.2) at Screening (V1).
6. Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, at Screening or at Baseline, or; (2) suicidal behaviors within the past year, or; (3) clinical assessment of significant suicidal risk during participant interview.
7. Depression secondary to other severe medical conditions according to clinicians' judgement.
8. Other personal circumstances and behavior judged to be incompatible with establishment of rapport or safe exposure to psilocybin, including exposure to psilocybin within the past year and use of psychedelics, such as ayahuasca, during the current depressive episode.

General Medical Exclusion Criteria:

9. Women who are pregnant, nursing, or planning a pregnancy. Male and female participants who are sexually active must agree to use a highly effective contraceptive method throughout their participation in the study. Women of child bearing potential must have a negative urine pregnancy test at Screening (V1) and Baseline (V2, Day -1).
10. Cardiovascular conditions: recent stroke (<1 year from signing of ICF), recent myocardial infarction (<1 year from signing of ICF), hypertension (blood pressure >140/90 mmHg) or clinically significant arrhythmia within 1 year of signing the ICF.

11. Uncontrolled or insulin-dependent diabetes.
12. Seizure disorder.
13. Positive urine drug screen for illicit drugs or drugs of abuse at Screening (V1) and Baseline (V2, Day -1). 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 the MM.
14. Current enrolment in any investigational drug or device study or participation in such within 30 days prior to Screening (V1).
15. Current enrolment in another clinical study of an investigational medical or participation in such within 30 days of Screening (V1).
16. Abnormal and clinically significant results on the physical examination, vital signs, ECG or laboratory tests at Screening (V1).
17. 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 outpatients and will be recruited primarily from general practitioners and specialised psychiatric services. Those participants considered eligible for the study will be further assessed to confirm eligibility after the participant has signed an ICF. 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. The investigator may call the MM to discuss the eligibility of any given participant.

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 outpatients and will primarily be recruited from general practitioners and specialised 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 – Visit 1

The participant will be seen initially to evaluate suitability for the study.

At the 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 concomitant medications
- Review of inclusion/exclusion criteria (Section 5)
- MINI 7.0.2
- HAM-D-17
- MGH-ATRQ
- C-SSRS (last 12 Months)
- MSI-BPD
- QIDS-SR-16
- Vital signs (ie, sitting blood pressure, pulse, body temperature, and respiratory rate)
- Physical examination, including weight and height

- 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
- AEs and SAEs (Sections 9 and 10)

Once a participant completes all Screening (V1) assessments and all screening data is entered into the EDC, the MM and CAT will review data entered and issue approval, if the participant is eligible.

Before the participant progresses further in the screening period (ie, before they attend Visit 1a), the PI will receive 2 email notifications, 1 from the MM and 1 from the CAT group, to confirm eligibility. Once these notifications are received (and the participant is deemed eligible), the participant can proceed to the next visit (V1a). Patients cannot begin psychoeducation or tapering off their antidepressant medication until they attend the clinic for the screening visit V1a.

At subsequent screening period visits (V1a, V1b), medications taken and any changes in medications since the previous visit, and the C-SSRS will be obtained.

6.2.2 Baseline Visit – Visit 2 – Day -1

The Baseline visit (V2, Day -1) should occur after Screening (V1) + < 7-Day window. At the Baseline visit (V2, Day -1), 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. The Baseline visit (V2, Day -1) should occur the day before the anticipated psilocybin session.

The following procedures will be performed and recorded at this visit:

- MADRS conducted by remotely located, independent raters
- HAM-D-17
- CGI-S

- MARS-5
- C-SSRS (Since Last Visit)
- GAD-7
- EQ-5D-3L (administered to both participant and caregiver; the latter is not mandatory)
- PANAS
- QIDS-SR-16
- Vital signs (ie, sitting blood pressure, pulse, body temperature, and respiratory rate)
- Urine samples for:
  - Urinalysis
  - Urine drug screen
  - Urine pregnancy test for all women of childbearing potential
- Medications taken and any changes in medications since the previous visit
- AEs and SAEs (Sections 9 and 10)

If the participant remains eligible, arrange for the participant to return to the study site for investigational product (IP) administration the next day.

After baseline data is entered into EDC, the CAT team will complete a final review to ensure the participant's continued eligibility. Participants cannot be progressed to V3 until this approval is received.

6.2.3 Visit 3 – Day 0 – Psilocybin Session

A preparation session with the therapist is always conducted the day before the psilocybin session, even if the psilocybin session is not conducted the day after Baseline (V2, Day -1). If the participant is out of the +≤ 7-day window, all baseline assessments are to be repeated. At the psilocybin session (the day of IP administration), the following are to be obtained:

- Vital signs (ie, continuous blood pressure throughout the session, pulse, body temperature, and respiratory rate)

- Administer IP (Section 8.3). The psilocybin session may be video recorded for training and adherence monitoring. A full description of the activities of the psilocybin session is found in the Therapist Manual. After the acute effects of the psilocybin pass, participants will be accompanied home.
- 5D-ASC
- C-SSRS (Since Last Visit)
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AEs and 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 conducted by remotely located, independent raters
- CGI-S
- CGI-I
- C-SSRS (Since Last Visit)
- GAD-7
- PANAS
- QIDS-SR-16
- Vital signs (ie, sitting blood pressure, pulse, body temperature, and respiratory rate)
- 12-lead ECG
- Blood samples for clinical laboratory tests
- Urine sample for urinalysis
- Medications taken and any changes in medications since the previous visit
- AEs and SAEs (Sections 9 and 10)

6.2.5 Visits 5 and 6 – 1 and 2 Week Postdosing

The participant will visit the clinic 1 week (7 days ± 1 day) and 2 weeks (14 days ± 1 day) following IP administration; the following assessments will be obtained at this visit:

- MADRS conducted by remotely located, independent raters
- CGI-S
- CGI-I
- MARS-5
- C-SSRS (Since Last Visit)
- GAD-7
- EQ-5D-3L (administered to participant)
- QIDS-SR-16
- Medications taken and any changes in medications since the previous visit
- AEs and SAEs (Sections 9 and 10)

6.2.6 Visit 7 – 3 Weeks Postdosing – End of Study

The participant will visit the clinic 3 weeks (21 days ± 1 day) following IP administration for the End of Study (EOS) visit; this visit is also to be completed if the participant is discontinued from the study early (early termination [ET]). The following assessments will be obtained at this visit:

- MADRS conducted by remotely located, independent raters
- CGI-S
- CGI-I
- MARS-5
- C-SSRS (Since Last Visit)
- GAD-7
- EQ-5D-3L (administered to both participant and caregiver [the latter is not mandatory])

- QIDS-SR-16
- Blood samples for clinical laboratory tests
- 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 ET should be documented and the V7 (EOS) procedures should be performed as noted in Section 6.2.6.

A termination electronic Case Report Form (eCRF) page should be completed for every participant who is enrolled, 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*
- *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 desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the participant gave a reason for withdrawing, it should be recorded in the eCRF.
- *Protocol Violation*: The participant's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (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.
- *Non-compliance:* The participant was non-compliant with study visits or procedures.

- *Other*: The participant was discontinued for a reason other than those listed above, such termination of study by the sponsor.

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Efficacy Assessments

All measures below will be captured electronically.

7.1.1 Montgomery-Asberg Depression Rating Scale

MADRS evaluations will be performed by an independent remote rater at Baseline (Day -1), Day 1 and Weeks 1, 2 and 3 (V2, V4, V5, V6 and V7, 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.[21] The structure of the telephone-based interview will be controlled through the use of The Structured Interview Guide for the MADRS (SIGMA),[34] which provides structured probes to ensure standardisation of administration and comprehensive coverage of 10 questions.

7.1.2 Clinical Global Impression – Severity Scale

The CGI-S is a 7-point scale that measures the severity of symptoms in patients with mental disorders.[2,12] It requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Ratings range from “normal, not at all ill” (1) to “among the most extremely ill patients” (7). This will be obtained at Baseline (Day -1), Day 1, and Weeks 1, 2 and 3 (V2, V4, V5, V6 and V7, respectively).

7.1.3 Clinical Global Impression – Improvement Scale

The CGI-I is a 7-point scale that requires the clinician to rate how much the patient’s symptoms have improved relative to a baseline state.[2,12] Ratings range from “very much improved” (1) to “very much worse” (7). This will be obtained at Day 1 and Weeks 1, 2 and 3 (V4, V5, V6, and V7, respectively).

7.1.4 Quick Inventory of Depressive Symptomatology – Self Rated – 16 Item

The 16-item QIDS is 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.[25] 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 nine symptom domains. The QIDS-SR-16 will be collected at every clinic visit or contact with the participant.

7.1.5 Generalised 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.[27] Participants choose one of four severity scores associated with problems related to the common anxiety disorders and then indicates 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 with a maximum score of 21. The GAD-7 will be obtained using the electronic patient-reported outcome (ePRO) device at Baseline (Day -1), Day 1 and Weeks 1, 2 and 3 (V2, V4, V5, V6 and V7, respectively).

7.1.6 EuroQoL-5-dimension 3-level Scale

The 3-level EQ-5D version (EQ‑5D‑3L) was introduced by the EuroQoL Group in 1990.[18,29] The EQ-5D-3L essentially consists of two sections: the EQ-5D-3L descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems and extreme problems. The participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the participant's health state.

The EQ VAS records the participant's self-rated health on a vertical visual analog scale (VAS), where the endpoints are labelled 'The best imaginable health state' and 'The worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflect the participant's own judgement.

The EQ-5D-3L will be obtained at Baseline (Day -1) and Week 3 (V2 and V7, respectively). Administration to a caregiver is not mandatory.

7.2 Safety Assessments

7.2.1 Columbia-Suicide Severity Rating Scale

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

The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior over a specified time period. The measurement of suicidal ideation is based on 5 "yes" or "no" questions with accompanying descriptions arranged in order of increasing severity. If the participant answers "yes" to either questions 1 or 2, the intensity of ideation is assessed in

5 additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behavior is assessed by asking questions categorizing behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and nonsuicidal self-injurious behavior.

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

A significant risk of suicide is defined as a "yes" in answer to (a) questions 4 or 5 on the suicidal ideation section; or (b) any questions on any item in the suicidal behavior section. This must be reported as an AE or SAE as appropriate and followed up accordingly. Additionally, if a participant responds "yes" to any of the suicidal ideation questions 1 through 3, the investigator should apply clinical judgment to determine the need for reporting this as an AE or SAE and the need for any appropriate referral.

The C-SSRS will be collected at every clinic visit.

7.2.2 Vital Signs

Respiratory rate, blood pressure, body temperature, and pulse rate will be obtained at Screening, Baseline (Day -1), Day 0, and Day 1 (V1, V2, V3, and V4, respectively).

Blood pressure will be monitored continuously throughout the psilocybin session. At all other clinic visits, blood pressure will be measured supine, after at least 5 min at rest. The three measurements should be recorded 1 to 2 min apart, and the results averaged to inform eligibility.

7.2.3 Electrocardiogram

Standard 12-lead ECGs will be obtained at Screening (V1) and Day 1 (V4).

7.2.4 Clinical Laboratory Tests

Blood samples will be obtained at Screening (V1), Day 1 (V4), and Week 3 (V7) for the following:

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

- *Chemistry:* albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (direct, indirect, and total), calcium, chloride, creatine kinase, creatinine, gamma-glutamyltransferase, glucose,

lactate dehydrogenase, lipase, magnesium, phosphate, potassium, protein-total, sodium, urea (blood urea nitrogen), and uric acid.

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

- *Urinalysis:* a dipstick urinalysis will be performed for blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, and urobilinogen.
- *Urine Drug Screen:* for illicit drugs or drugs of abuse at Screening (V1) and Baseline (V2, Day -1). 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, Day -1).

Laboratory samples will be analysed by a central laboratory (Eurofins) to ensure consistent interpretation of results. Instructions for shipment of samples and review of results is provided in the Laboratory Manual. 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.

7.2.5 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 V7 (EOS/ET) will be followed until resolution or no longer considered clinically significant by the investigator.

See Sections 9 and 10 for additional information.

7.3 Other Assessment Instruments

7.3.1 Hamilton Depression Rating Scale – 17-item

The HAM-D-17, a 17-item scale, is used to measure the degree of symptom severity in depressed patients.[13] The HAM-D-17 rating will be performed by the investigator using the electronic clinical outcome assessment (eCOA) device at the Screening (V1) and Baseline (V2, Day -1) 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.[33] This will be captured electronically.

7.3.2 Mini International Neuropsychiatric Interview, Version 7.0.2

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 DSM-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.[26]

At Screening (V1), participants will be assessed for MDD, as documented by DSM-5 criteria, and the lack of other psychiatric diagnoses will be confirmed by use of the MINI.[26]

7.3.3 Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire

The MGH-ATRQ is a self-rated scale used to determine treatment resistance in major depressive disorder.[5] 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 study and examines the participants' antidepressant history to identify pseudo-resistance and treatment resistance. Failure to respond to an adequate dose and duration of 2, 3, or 4 pharmacological treatments for the current episode, as determined through the MGH-ATRQ, and using the supplementary advice on additional antidepressants are not included in MGH-ATRQ (Appendix III). Augmentation with an add on treatment counts as a second treatment, provided it is approved for the adjunctive treatment of MDD in that country. In addition, a list of recently approved antidepressant medications not included in MGH-ATRQ will be provided to investigators. The MGH-ATRQ will be collected at Screening (V1) only. This will be captured electronically.

7.3.4 McLean Screening Instrument for Borderline Personality Disorder

The MSI-BPD is a commonly used measure to assess for BPD.[35] The scale consists of 10 items based on the DSM-5 BPD criteria; the first eight items represent the first eight criteria in the DSM-5 for BPD diagnosis, while the last two questions assess the paranoia and dissociation criteria for BPD. Scores for the MSI-BPD range from 0 to 10, with each item rated as "1" if present and "0" if absent. A score of 7 or higher indicates a likelihood for the participant to meet criteria for BPD. The MSI-BPD will be collected at Screening (V1) only. This will be captured electronically.

7.3.5 Five Dimension Altered States of Consciousness Questionnaire

The 5D-ASC measures the acute drug effects using five primary dimensions and respective subdimensions to assess alterations in mood, perception, and experience of self in relation to environment and thought disorder. The five dimensions include: oceanic boundlessness, anxious ego dissolution, visionary restructuralization, auditory alterations, and reduction of vigilance.[8,9,28] This will be administered immediately after the psilocybin session on Day 0 (V3). This will be captured electronically.

7.3.6 The Positive and Negative Affect Schedule

The PANAS measures the acute emotional drug effects, and comprises two mood scales that measure positive and negative affect.[32] Participants respond to 20 items using a 5-point scale that ranges from "slightly or not at all (1)" to "extremely (5)". A total higher score on the positive affect questions indicates more of a positive affect while a lower score on the negative affect questions indicates less of a negative affect. This will be administered at Baseline (V2, Day -1) and the day after the psilocybin session (V4) This will be captured electronically.

7.3.7 Medication Adherence Report Scale

The MARS-5 is a 5-item self-report scale of medication adherence.[6,19] Participants respond to five statements regarding how often they engage in non-adherent behaviors in relation to their SSRI medication on a 5 point Likert scale (from "always" to "never"). The item scores are summed to indicate overall level of adherence. This will be administered at Baseline (V2, Day -1) and Weeks 1, 2 and 3 (V5, V6 and V7, respectively).

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 as having a serious impact on the efficacy results will lead to the relevant participant being excluded from the analysis.

Protocol deviations will be summarised by sites 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 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	Catalent Pharma Solutions, 8 Orchard Place, Nottingham Business Park, Nottingham, NG8 6PX, UK
Dose	25 mg
Route	Oral
Formulation	Capsule
Strength	5 mg

8.1.1 Formulation

Matching psilocybin capsules 5 mg are manufactured by Catalent Pharma Solutions, Nottingham, UK.

8.1.2 Storage

All IP must be kept in a locked area with limited access. The high-density polyethylene (HDPE) bottles of IP are to be stored as indicated in the IP Handling Manual. Deviations of storage temperature outside this required range should be documented and the sponsor or its designee should be notified promptly. Bottles of IP should not be frozen. If any component of the IP is damaged, the sponsor or its designee must be notified as soon as possible.

8.2 Packaging and Blinding

Psilocybin capsules are packaged into HDPE bottles 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). Each bottle contains five 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. Refer to the IP Handling Manual for additional details.

8.3 Dose and Administration

Study drug will be administered simultaneously to up to six participants.

Each participant will receive 1 x 25 mg treatment bottle containing 5 x 5 mg capsules.

After a light breakfast taken at least 2 h prior to dosing and under observation of study staff, the 5-capsule dose is to be swallowed with a full glass of water; due to the number of capsules in a dose, additional water will be provided as necessary to swallow the dose. Study staff will ensure the entire 5-capsule dose has been swallowed.

To prepare for the drug experience, the participant will take the IP and lie down on a couch or bed in a room with dim lights and a standard playlist of relaxing music playing quietly. The trained therapist will be present with the participant at all times.

The effects of psilocybin usually start about 20 to 30 min after administration, becoming most intense in the first 90 to 120 min, and gradually subside in 5 to 6 h. The participants will be asked to remain in the room for the duration of the session regardless of the intensity of the effects, prefreably lying down and mostly silent unless they have a concern or need to communicate a discomfort or seek reassurance from the therapist, or use the restroom. The therapist will 'check-in' with the participant (ie, ask how the participant is doing) in 30 to 60 min intervals postdosing. A light meal and fruit will be available for the participant.

About 5 to 6 h after dosing, a trained therapist will discuss the IP administration experience with the participant. The participant is to be discharged 6 to 8 h postdosing when, in the opinion of the investigator, the acute effects of psilocybin are resolved. The participant will then be accompanied home. The site is to be notified that they have returned home safely, and in the absence of receiving a phone call, site staff will directly contact the participant.

8.4 Accountability

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

8.5 Concomitant Therapy

All prescription and nonprescription medications (eg, over-the-counter [OTC] 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 and therapies will be assessed and recorded in the eCRF during each study visit. All as-needed (*pro re nata*, PRN) prescriptions should be converted to reflect actual number of pills or dose taken per day.

8.5.1 Permissible Medications

Participants must have been receiving treatment with a SSRI (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram or escitalopram) at an adequate dose according to local recommendations for at least 6 weeks before Screening (V1) and Baseline (V2, Day -1). Dose changes within the adequate range are acceptable. We recommend that the participant is continued on the SSRI for the duration of the follow-up period of the study, ideally at the same dose.

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 (V7, EOS), participants are permitted to use 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; zopiclone for sleep disorders) should be used no more than two times a week and not in the 12 h before any study assessment. Documentation of the use of adjunctive anxiolytics, hypnotics or medication with potential psychotropic properties (including OTC preparations) will be obtained at each clinic visit.

Therapy considered necessary for the participant's welfare may be given at the discretion of the study clinician. If the permissibility of a specific medication/treatment is in question, please contact the sponsor or its designee.

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

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopasusal unless permanently sterilised (ie, participant had 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 devise
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Periodic abstinence (ie, calendar, symptothermal, or postovulation methods, and tubal ligation/occlusion) is 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 sponsor or Worldwide immediately after the pregnancy is confirmed according to Section 12.5.

8.5.3 Prohibited Medications

Participants are to be discontinued from antidepressant and/or antipsychotic medications, except the participants SSRI (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram or escitalopram), at least 2 weeks prior to Baseline (V2, Day -1). These medications include the following two classes of the Anatomical Therapeutic Chemical (ATC) Classification System: NO5A Antipsychotics & NO6A Antidepressants. Methylphenidate (ATC Classification System: NO6B Psychostimulants) is also excluded.

The MM should be contacted if there is any question that a used medication is thought to be in one of these classes. These medications are not to be reintroduced to the participant until after V7 (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 per local site practice 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, cognitive behavioral therapy whose therapeutic intention is remediation of the depressive episode.

Because the anticipated half-life of psilocybin is approximately 3 h, and only one administration of test product is permitted, no known issues regarding pharmacokinetic or pharmacodynamic interactions are envisioned within approximately 7 days of product administration.

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 whether the monitors and responsible physician judge that they are capable of maintaining the safety of the participant 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; the oral route is preferable because intravenous (IV) injection procedures may further exacerbate the participant's anxiety).

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

In case of development of acute anxiety or psychotic symptoms requiring pharmacological intervention, the participant will be managed appropriately. Rescue medication should be administered according to their respective approved prescribing information and dose levels. The participant may be discharged from the clinic when, in the opinion of investigator, the condition has stabilized. The participant will be accompanied home. 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 for how to manage participants during difficult psychological states are detailed in the Therapist Manual.

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 eCRF, 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 sponsor or Worldwide of all SAEs and nonserious AEs occurring during the clinical study so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the product under clinical investigation are met.

The sponsor or Worldwide has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The sponsor or Worldwide will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators. These will be detailed in the safety plan.

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 eCRF.

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.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

The investigator should report all AEs on the AE page(s) of the eCRF 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 two 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 Action Taken Regarding Investigational Product

Dose modifications of IP (ie, dose not changed, drug withdrawn, drug interrupted, or dose increased) are not applicable as this is a single dose study.

- Not Applicable: Participant died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

9.5 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 = Hospitalisation or prolongation of hospitalisation required (ie, hospitalisation was required or prolonged because of the AE, whether medication was required)

4 = Other

9.6 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

9.7 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 eCRF:

- 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.

9.8 Overdose

Any instance of overdose (suspected or confirmed) must be communicated to Worldwide or a specified designee 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 Events of Special Interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the study drug, for which ongoing monitoring and immediate notification by the investigator to the sponsor is required. Such AEs may require further investigation to characterize and understand them.

The following events will be reported as AESI:

- Euphoric mood
- Dissociative disorder
- Hallucination
- Psychotic disorder
- Cognitive disorder
- Disturbance in attention
- Mood altered
- Psychomotor skills impaired
- Inappropriate affect
- Overdose
- Intentional product misuse

The investigator must report to the sponsor all the above events on the eCRF page within 24 h of learning about the event regardless of relationship to study drug.

The report should include the following minimum information:

- Participant number
- Event
- Date/time of onset
- Duration of the event
- Dose of drug taken
- Severity
- Outcome

All AESIs will be followed until resolved or stable.

9.10 Adverse Event Follow-up

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

If the investigator detects an AE in a study participant after the last scheduled follow-up visit and considers the event possibly related or related to prior study treatment, the investigator should report it to Worldwide.

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 hospitalisation or prolongation of existing hospitalisation
- 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 hospitalisation, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise 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 hospitalisation
  - 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.

Hospitalisation: AEs requiring hospitalisation should be considered SAEs. Hospitalisation 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, hospitalisation signifies that the participant has been detained (usually involving at least one 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 'hospitalisation' 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 Worldwide and to the IRB/IEC 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 Worldwide.

The investigator must report to the sponsor all SAEs on the eCRF page within 24 h of learning about the event regardless of relationship to IP.

All information about SAEs will be collected and reported via the SAE form and sent by email message or facsimile (contact information will be contained in the investigator site file). The investigator should send the initial report within 24 h of becoming aware of the SAE. At minimum, the initial report should include the following information:

- Event
- Study code
- Participant identification number, initials, and date of birth
- IP
- Reporter name and contact information

If the site experiences a temporary disruption of the eCRF system, a back-up paper SAE Report Form will be available for site staff to complete.

- Site staff will complete the paper SAE report form and email it within 24 h to the following address: drugsafety@worldwide.com

- In cases where the email system is unavailable, site staff will send the SAE by fax to: +1-866-387-5539 (US) and +44 208 043 4813 (ROW).

If notification is made via email or fax, site staff must enter the SAE information into the eCRF system as soon as the system becomes available. Should a back-up SAE form be used, the original SAE form should be kept at the study site.

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). Additional follow-up information must be reported in the eCRF within 24 h of awareness following investigator (or site) awareness of the information. The investigator should not delay reporting an SAE in order to obtain additional information. Additional information, when available, should be reported per the reporting procedures described above.

All SAEs shall be followed until resolution, until the condition stabilises, or until the participant is lost to follow-up, or otherwise explained. Once the SAE is resolved, the corresponding AE eCRF 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.

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilisation and for reported deaths, the investigator should supply Worldwide and the IRB/IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. The sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

All SAEs will be followed until resolved or stable and the outcome documented on the eCRF.

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (those not listed in the IB) according to local regulatory requirements and the sponsor/Worldwide policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor or Worldwide will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

11 STATISTICS

11.1 General Procedures

The statistical analysis will be undertaken by Worldwide in collaboration with the sponsor. A detailed Statistical Analysis Plan (SAP) will be finalised and signed before database lock. Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report.

11.2 Sample Size

No formal sample size calculations were performed for this study. Approximately 20 participants are expected to be enrolled in the study.

11.3 Statistical Methods

The Safety Population will consist of all enrolled participants, 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 enrolled participants who also receive the dose of IP.

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

11.3.1 Efficacy and Outcome Measures

- MADRS
- CGI-S
- CGI-I
- EQ-5D-3L (participant and caregiver; the latter is not mandatory)
- QIDS-SR-16
- GAD-7
- PANAS
- 5D-ASC
- C-SSRS

11.3.2 Analysis of Efficacy

Since this is a single treatment open-label study, no statistical testing will be performed. The FAS and the PP populations will both be used for each secondary endpoint, if the two sets are not identical. For each of the secondary endpoints (MADRS, CGI-S, C-SSRS), measuring change from Baseline to Week 3, summary statistics will be provided.

Analysis of exploratory endpoints will be detailed in the SAP.

11.3.3 Multiplicity

Not applicable.

11.3.4 Analysis of Safety

Safety data will be presented for the Safety Population. Safety will be evaluated based on AEs, ECGs, clinical laboratory tests, vital signs and suicidal ideation/behavior (measured using C-SSRS).

11.3.4.1 Columbia-Suicide Severity Rating Scale

Item scores from the C-SSRS for all visits, the item scores from the version assessing suicidality since the last visit, and all postbaseline visits (V3 to V7, inclusive) by treatment will be tabulated. Summary statistics of suicidal ideation and suicidal behavior following IP administration will be presented.

11.3.4.2 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 summarised by treatment group, and by severity and relationship to IP. Serious AEs and AEs leading to withdrawal from the study will be tabulated.

A treatment-emergent adverse event (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 summarised 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.

11.3.4.3 Electrocardiographic Data

The ECG data will be summarised descriptively based on measures of change in each ECG parameter from Screening (V1) to post-treatment (V4). Frequency tabulations of the abnormalities will be provided. ECG variables to be analysed will include heart rate, PR interval, QRS interval, QT interval, and corrected QT interval using the following correction methods: QT corrected according to Bazett's formula and QT corrected according to Fridericia's formula.

11.3.4.4 Laboratory Data

Laboratory data (haematology and blood chemistry parameters) will be presented for each treatment group using descriptive statistics, including mean and mean change from baseline values at each scheduled time point. Shift tables will display numbers of participants with normal/abnormal values at Baseline versus post-treatment. The frequency of laboratory abnormalities will be tabulated. By-participant data listings will flag laboratory values that are outside normal reference ranges or markedly abnormal findings.

11.3.4.5 Vital Signs

Changes from Baseline in vital signs, blood pressure (systolic and diastolic), body temperature, pulse rate, and respiratory rate, will be summarised 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 summarised. A listing of weight and height at Screening (V1) will be provided.

11.3.5 Demographic and Baseline Characteristics

Participant demographics and baseline characteristics will be summarised using descriptive statistics, no formal statistical analysis tests will be performed.

11.4 Interim Analysis

No interim analysis is planned.

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 CFR 312), ICH guidelines for Good Clinical Practice (GCP), the regulations on electronic records and electronic signature (21 CFR 11), and the most recent guidelines of the Declaration of Helsinki (Appendix II). These guidelines are on file at Worldwide.

The study will also be performed in accordance with any laws and regulations in force in the country in which 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 authorisation 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

Sponsor 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.

Sponsor 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 eCRF pregnancy form within 24 h of becoming aware of the event. Exposure in Utero (EIU)

Reporting form. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The investigator should make every effort to follow the participant until completion of the pregnancy and complete the EIU Reporting form eCRF with complete pregnancy outcome information, including normal delivery and 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. In the event the eCRF system is unavailable, a back-up paper Pregnancy Reporting Form will be available for site staff to complete following the reporting guidelines as outlined in Section 10.2.

For reports of pregnancy in the partner of a male participant, the pregnancy eCRF page EIU form (or SAE form if associated with an adverse outcome) should be completed with the participant's identification 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

By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, 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 eCRF 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 study. The eCRF itself is not to be used as a source document under any circumstances.

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. In addition, because this is an international study, the retention period must meet the requirements of the most stringent authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

13 AUDITING AND MONITORING

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, GCP guidelines, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each participant.

Medical advisors and clinical research associates or assistants may request to witness participant evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organised by the sponsor to assure acceptable protocol execution. The study may be audited by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required participant records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

14 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by the sponsor. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. The sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or the sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the participant and/or has an impact on the participant's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for participants enrolled in the study before continued participation.

15 STUDY REPORT AND PUBLICATIONS

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of the sponsor is discussed in the investigator's Clinical Research Agreement.

16 STUDY DISCONTINUATION

Both the sponsor and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, the sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, the sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

17 CONFIDENTIALITY

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

Identification of participants and CRFs shall be by initials and participant identification number only. If required, the participant's full name may be made known to an authorised regulatory agency or other authorised official.

18 REFERENCES

1. Brown RT, Nicholas CR, Cozzi NV, et al. Pharmacokinetics of escalating doses of oral psilocybin in healthy adults. *Clin Pharmacokinet.* 2017;56(12):1543-1554. doi 10.1007/s40262-017-0540-6.
2. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)*. 2007 Jul;4(7):28-37.
3. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet.* 2016;3(7):619-627.
4. Carhart-Harris RL, Roseman L, Bolstridge M, et al. Psilocybin for Treatment-Resistant Depression: fMRI-Measured Brain Mechanisms. Sci Rep 2017; 7(1):13187. doi: 10.1038/s41598-017-13282-7.
5. Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. Validation of the Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire (ATRQ*). CNS Neurosci Ther*. 2010;16(5):322-325.
6. Clatworthy J, Bowskill R, Parham R, Rank T, Scott J, Horne, R. Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. *J Affect Disord*. 2009; 116(1–2):51-55.
7. COMPASS Pathways Limited. Investigator's Brochure for Psilocybin. 2018.
8. Dittrich A. The standardized psychometric assessment of alter states of consciousness (ASCs) in humans. *Pharmacopsychiatry.* 1998;31(Suppl 2):80-84.
9. Dittrich A, Lamparter D, Maurer M. 5D-ABZ: Fragebogen zur Erfassung Aussergewöhnlicher BewusstseinszustäEine kurze Einführung. [5D-ASC: questionnaire for the assessment of altered states of consciousness. A short introduction]. PSIN Plus Publications. 2006.
10. Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, et al. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and D-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. *Psychopharmacology* (Berl). 1999b;142(1):41-50.
11. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology* (Berl). 2011;218(4):649-665.
12. Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976.
13. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-62. doi:10.1136/jnnp.23.1.56. PMID: 14399272.

14. Hasler F, Bourquin D, Brenneisen R, Bar T, Vollenweider FX. Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. *Pharm Acta Helv.* 1997;72(3):175-184.

15. Hasler F, Bourquin D, Brenneisen R, Vollenweider FX. Renal excretion profiles of psilocin following oral administration of psilocybin: a controlled study in man. *J Pharm Biomed Anal.* 2002;30(2):331-339.

16. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology* (Berl). 2004;172(2):145-156.

17. Hasler F. Untersuchungen zur Humanpharmakokinetik von Psilocybin. Berne: University of Berne (Switzerland). 1997.

18. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20(10):1727-1736.

19. Horne R. The nature, determinants and effects of medication beliefs in chronic illness. 1997. PhD Thesis. University of London.

20. Lindenblatt H, Kramer E, Holzmann-Erens P, Gouzoulis-Mayfrank E, Kovar KA. Quantitation of psilocin in human plasma by high-performance liquid chromatography and electrochemical detection: comparison of liquid-liquid extraction with automated on-line solid-phase extraction. *J Chromatogr B Biomed Sci Appl.* 1998;709(2):255-263.

21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.

22. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. *Addict Biol.* 2002;7(4):357-364.

23. Passie T. A history of the use of psilocybin in psychotherapy. In: Metzner R, editor. Sacred mushroom of visions: Teonanácatl: a sourcebook on the psilocybin mushroom. Rochester, Vermont: Park Street Press; 2005. p. 113-138.

24. Rickli A, Moning OD, Hoener MC, Liechti ME. Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens. *Eur Neuropsychopharmacol.* 2016;26(8):1327-1337.

25. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item quick inventory of depressive symptomatology (QIDS) clinician rating (QIDS-C) and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54 (5):573-583.

26. Sheehan DV, Giddens JM, Sheehan IS. Status update on the Sheehan-suicidality tracking scale (SSTS) 2014. *Innov Clin Neurosci*. 2014 Sep-Oct;11(9-10):93-140.

27. Spitzer RL, Kroenke K., Williams, JB, Lowe, B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.

28. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PLoS One*. 2010;5(8): e12412.

29. The EuroQol Group. Euroqol-a new faciltiy for the measurement of health–related quality of life. *Health Policy.* 1990;16(3):199-208.

30. Tylš F, Páleníček T, Horáček J. Psilocybin-summary of knowledge and new perspectives. *Eur Neuorpsychopharmcol*. 2014 Mar;24(3):342-356.

31. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D. Psilocybin induces Schizophrenia-Like Psychosis in Humans via a Serotonin-2 Agonist Action. *Neuroreport. 1998;* 9(17):3897-3902.

32. Watson D, Clark LA, and Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psyhchol.* 1988;54(6):1063-1070.

33. Williams JB. A structured interview guide for the Hamilton depression rating scale. *Arch Gen Psychiatry*. 1988;45(8):742-747.

34. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). *Br J Psychiatry*. 2008;192(1):52-58.

35. Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). *J Pers Disord.* 2003;17(6):568-573.

19 APPENDICES

19.1 Appendix I – Names of Study Personnel

Sponsor:	Hans Eriksson, MD, PhD, MBA Chief Medical Officer COMPASS Pathways, Ltd 16 Old Bailey London, England, EC4M 7EG UK Telephone: +44 (0) 79 2087 6562 (UK) +1 (516) 805 3533 (US)
Medical Monitor:	Olga Kolotilina, Medical Director, Medical Affairs Worldwide Clinical Trials Kemerovo, 650065, Russia Telephone: +7 906 925 1812 (mobile) +7 812 346 8247, #1504 (office) +7 812 346 8248 (fax)
Clinical Research Organisations:	Worldwide Clinical Trials 3800 Paramount Parkway, Suite 400 Morrisville, NC 27560 Telephone: +1 (919) 674 2900
Central Laboratory:	Eurofins Central Laboratory B.V. Bergschot 71 4817 PA Breda The Netherlands Telephone: +31 76 573 75 21 +31 76 573 77 76 (fax)
Investigational Product Distribution:	Fisher Clinical Services UK Ltd Langhurstwood Road, Horsham, West Sussex, RH12 4QD, UK Telephone: +44 (0) 1403 224308

19.2 Appendix II – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles

for

Medical Research Involving Human Participants

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DS, USA, October 2002

55th WMA General Assembly, Tokyo, Japan, October 2004

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

and the

64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human participants. Medical research involving human participants includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my participant will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the participant's interest when providing medical care which might have the effect of weakening the physical and mental condition of the participant."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human participants.

In medical research on human participants, considerations related to the well being of the human participant should take precedence over the interests of science and society.

The primary purpose of medical research involving human participants is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is participant to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be participant to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal and regulatory requirements for research on human participants in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human participants set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human participant.

Medical research involving human participants must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human participants should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing studies. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for participants.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human participants should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human participant must always rest with a participant of the research, even though the participant has given consent.

Every medical research project involving human participants should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the participant or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human participants unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human participants should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the participant. This is especially important when the human participants are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The participants must be volunteers and informed participants in the research project.

The right of research participants to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the participant, the confidentiality of the participant's information and to minimise the impact of the study on the participant's physical and mental integrity and on the personality of the participant.

In any research on human beings, each potential participant must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The participant should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the participant has understood the information, the physician should then obtain the participant's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the participant is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research participant who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a participant deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research participants with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the participants who are research participants.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every participant entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the participant which aspects of the care are related to the research. The refusal of a participant to participate in a study must never interfere with the participant-physician relationship.

In the treatment of a participant, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the participant, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

19.3 Appendix III – Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire – Additional Detail Regarding the Assessment of Previous Antidepressant Treatment

The Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire (MGH-ATRQ) scale elicits information regarding prior antidepressant use. Additional drugs with regulatory approval for use in major depressive disorder in different countries are listed at the end of this document. Among these drugs are atypical antipsychotics approved for the treatment of major depressive disorder, as adjunctive treatments or as a monotherapy. The drug list may not be exhaustive.

For a drug treatment to be considered appropriate, it must have been administered at a dose approved for the treatment of major depressive disorder in the country where the study site is located. The minimum duration of treatment must be deemed appropriate by the investigator, and as a guidance, 6 to 8 weeks can often be considered as an adequate treatment duration.

Some drugs are occasionally dosed based on therapeutic drug monitoring results. Prior use of drugs approved for major depressive disorder using therapeutic drug monitoring should be considered an appropriate intervention, if the concentrations are within the target range, irrespective of dose, and if the duration is considered adequate.

Antidepressants, if administered at an adequate dose and duration, can support a characterisation of Treatment-Resistant Depression (TRD), in addition to medications listed in the (MGH-ATRQ).

Tri- and tetra-cyclic antidepressants

Noveril	Dibenzepin
Prothiaden	Dosulepin
Gamanil	Lofepramine
Sintamil	Nitroxazepine
Insidon	Opipramol
Asendin	Amoxapine
Tecipul	Setiptiline

MAO inhibitors

Humoryl	Toloxatone
Celeport	Bifemelane

Other antidepressants

Spravato	Esketamine
Brexanolone	Zulresso
Sediel	Tandospirone

Atypical antipsychotics

Abilify	Aripiprazole
Rexulti	Brexpiprazole
Zyprexa	Olanzapine
Seroquel	Quetiapine

Combination products

Etafron	Amitriptyline/perphenazine
Deanxit	Flupentixol/melitracen
Symbyax	Olanzapine/fluoxetine
Parmodalin	Tranylcypromine/trifluoperazine