(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 October 2020 (22.10.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/212952 A1

(51) International Patent Classification:
A61K 31/675 (2006.01) *A61P 25/30* (2006.01)
A61K 31/4045 (2006.01) *A61P 25/00* (2006.01)
A61P1/00 (2006.01) *A61P 25/06* (2006.01)
A61P 25/16 (2006.01) *A61P25/22* (2006.01)

(21) International Application Number:
PCT/IB2020/053688

(22) International Filing Date:
17 April 2020 (17.04.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

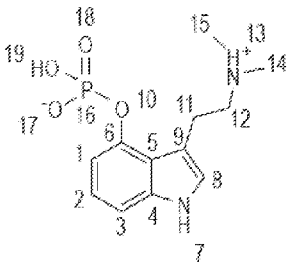
62/835,449	17 April 2019 (17.04.2019)	U S
62/835,450	17 April 2019 (17.04.2019)	U S
62/835,458	17 April 2019 (17.04.2019)	U S
62/835,460	17 April 2019 (17.04.2019)	U S
62/835,464	17 April 2019 (17.04.2019)	U S
62/835,465	17 April 2019 (17.04.2019)	U S
62/835,472	17 April 2019 (17.04.2019)	U S
62/835,474	17 April 2019 (17.04.2019)	U S
62/835,476	17 April 2019 (17.04.2019)	U S
62/835,477	17 April 2019 (17.04.2019)	U S
62/835,478	17 April 2019 (17.04.2019)	U S
62/835,479	17 April 2019 (17.04.2019)	U S
62/835,480	17 April 2019 (17.04.2019)	U S
62/835,481	17 April 2019 (17.04.2019)	U S
62/835,482	17 April 2019 (17.04.2019)	U S
62/835,484	17 April 2019 (17.04.2019)	U S
62/835,485	17 April 2019 (17.04.2019)	U S
62/893,1 10	28 August 2019 (28.08.2019)	U S
62/893,61 1	29 August 2019 (29.08.2019)	U S
62/946, 159	10 December 2019 (10. 12.2019)	U S

(71) Applicant: **COMPASS PATHFINDER LIMITED** [GB/GB]; 3rd Floor, 1 Ashley Road, Altrincham, Cheshire WA14 2DT (GB).

(72) Inventors: **LONDESBROUGH, Derek John;** 37 Linden Grove, Hartlepool, Durham TS26 9QA (GB). **BROWN, Christopher;** 30 Cherrytree Gardens, Gateshead, Tyne and Wear NE9 6TY (GB). **NORTHEN, Julian Scott;** 36 Hepscott Terrace, South Shields, Tyne and Wear NE33 4TH (GB). **MOORE, Gillian;** 22 Matfen Court, Sedgefield, Durham TS21 2JB (GB). **PATIL, Hemant Kashinath;** 137C Kingston Road, Leatherhead, Surrey KT22 7NT (GB). **NICHOLS, David E.;** 56702 Nash, Chapel Hill, NC 27517 (US). **CROAL, Megan;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **ERIKSSON, Hans Ake;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **GOLDSMITH, George;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrinch am Cheshire WA14 2DT (GB). **HICKEY, Molly Tabitha;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **HURLEY, Shaun;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **MALIEVSKAIA, Ekaterina;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **MARWOOD, Lindsey;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrinch am Cheshire WA14 2DT (GB). **MCCULLOCH, Drummond E-Wen Joe;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **MEDHURST, Laurie Emma;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrin-

(54) Title: TREATMENT OF DEPRESSION AND OTHER VARIOUS DISORDERS WITH PSILOCYBIN

Fig. 1



(57) Abstract: The disclosure provides methods for treating a subject in need thereof comprising administering to the subject a therapeutically -effective dose of psilocybin. The methods described herein may be used to treat a variety of diseases, disorders, and conditions. For example, the methods may be used to treat depression, neurocognitive disorders, autism spectrum disorder, and/or attention-deficit/hyperactivity disorder.

[Continued on nextpage]

WO 2020/212952 A1

chant Cheshire WA14 2DT (GB). **POULSEN, Nathan;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **SELIMBEYOGLU, Aslihan;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **SOULA, Anaïs;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **SHUXIANG, Amanda Tan;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **VERAART, Manon Cecile Elisabeth;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **WHELAN, Tobias Patrick;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **WILDE, Lars Christian;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB). **WRIGHT, Stephen;** c/o COMPASS Pathways Limited, 3rd Floor, 1 Ashley Road, Altrincham Cheshire WA14 2DT (GB).

(74) **Agent: COOLEY (UK) LLP;** Dashwood, 69 Old Broad Street, London EC2M IQS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, Cl, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

TREATMENT OF DEPRESSION AND OTHER VARIOUS DISORDERS WITH PSILOCYBIN

RELATED APPLICATIONS

This application claims priority to U.S. Application Serial Nos. 62/835,449; 62/835,450; 62/835,458; 62/835,460; 62/835,464; 62/835,465; 62/835,472; 62/835,474; 62/835,476; 62/835,477; 62/835,478; 62/835,479; 62/835,480; 62/835,481 ; 62/835,482; 62/835,484; and 62/835,485, all filed April 17 , 2019; U.S. Application Serial No. 62/893, 110 , filed August 28, 201 9 , U.S. Application Serial No. 62/893,61 1, filed August 29, 2019, and U.S. Application Serial No. 62/946,159, filed December 10, 2019, each of which is incorporated herein by reference in its entirety.

BACKGROUND

Depression is one of the most common mental illnesses, affecting more than 264 million people worldwide. It is characterized by depressed mood and markedly diminished interest or pleasure in activities. Other symptoms include significant weight loss or weight gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or indecisiveness, recurrent thoughts of death, suicidal ideation or suicidal attempts.

Current treatments for depression often consist of a combination of psychotherapy and one or more daily medications that regulate neurotransmitters such as dopamine, serotonin, and norepinephrine. These medications often take weeks to months to achieve their full effects and in the meantime, individuals continue to suffer from their symptoms and be at risk of self-harm, as well as harm to their personal and professional lives.

There remains a need in the art for an effective treatment for depression that provides a rapid onset of antidepressant effects within hours or a few days and is sustained long-term.

SUMMARY

Psilocybin may provide numerous clinical benefits, such as benefits in neural plasticity and cognitive function (as measured using e.g., Cambridge Neuropsychological Test Automated Battery (CANTAB) tests) with improvements in, for example, working memory and executive function, sustained attention, and episodic memory. These benefits have implications for psilocybin's use in the treatment of various diseases, disorders, and conditions, including both psychiatric and neurological aspects thereof.

In some embodiments, the disclosure provides a method of treating depression in a subject in need thereof, the method comprising administering an effective amount of psilocybin or an active metabolite thereof to the subject. In some embodiments, the subject has a major depressive disorder, atypical depression, bipolar disorder, catatonic depression, a depressive disorder due to a medical condition, postpartum depression, premenstrual dysphoric disorder, or seasonal affective disorder. In some embodiments, the subject has a depressive disorder that is resistant to treatment.

In some embodiments, the methods of the disclosure reduce at least one sign or symptom of depression. In some embodiments, the sign or symptom of depression is depressed mood, diminished interest in activities, weight loss or gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate or indecisiveness, or suicidal ideation or behavior.

In some embodiments, the sign or symptom of depression is measured according to a diary assessment, an assessment by clinician or caregiver, a clinical rating scale, or by functional MRI. In some embodiments, the functional MRI measures the amygdala blood oxygen level-dependent (BOLD) response in the subject.

In some embodiments, the sign or symptom of depression is measured using a clinical depression rating scale, wherein the clinical depression rating scale is a Quick Inventory of Depressive Symptomatology (QIDS)-16 scale, a QIDS-16 daily scale, a Hamilton Depression Rating scale, a Beck Depression Inventory scale, a Montgomery-Asberg Depression Rating Scale, a Clinical Global Impression Scale, a Zung Self-Rating Depression Scale, a Raskin Depression Rating Scale, and/or a Young Mania Rating Scale.

In some embodiments, the sign or symptom of depression is measured using a Spielberger's Trait and Anxiety Inventory, a Generalized Anxiety Disorder 7-Item Scale, a Warwick-Edinburgh Mental Wellbeing Scale, a Flourishing Scale, a Snaith Hamilton Anhedonia Pleasure Scale, a Life Orientation Test, a Meaning in Life Questionnaire, a Brief Resilience Scale, a Dysfunctional Attitudes Scale, a 44-item Big Five Inventory, a Peters 21-item Delusional Inventory, an Examination of Anomalous Self- Experience, a Ruminative Responses Scale, a White Bear Suppression Inventory, a Barrett Impulsivity Scale, a Brief Experiential Avoidance Questionnaire, a Modified Tellegen Absorption Questionnaire, a Scale to Assess Therapeutic Relationship, a Credibility/Expectancy Questionnaire, a Connectedness to Nature Scale, a Political Perspective Questionnaire, a Social Connectedness Scale, a Bech-Rafaelsen Mania Rating Scale, a Revised Santa Clara brief compassion scale, a Gratitude Questionnaire, a Short

Suggestibility Scale, a Rosenberg Self-Esteem Scale, a Universality Subscale of the Spiritual Transcendence Scale, an Oxford Questionnaire on the Emotional Side-effects of Antidepressants, a Lauks Emotional Intensity Scale, a Sexual Dysfunction Questionnaire, a Brief Index of Sexual Functioning for Women, a Sexual Perceptions Questionnaire, a Barnes Akathisia Rating Scale, a Work Productivity and Activity Impairment Questionnaire, a Work and Social Adjustment Scale, a Connectedness Questionnaire, a Standard Assessment of Personality, a Positive and Negative Syndrome Scale, a Mastery Insight Scale, a Self-Reflection and Insight Scale, a Psychological Insight Scale, a Metaphysical Beliefs Questionnaire, a Spiritual Bypassing Scale, an Adverse Childhood Experience Questionnaire, a Therapeutic Music Experience Questionnaire, a Setting Questionnaire, an Absorption in Music Scale, a Psychedelic Predictor Scale, a Surrender Scale, a EuroQOL-5 Dimension-3 Level Scale, a Columbia-Suicide Severity Rating Scale, a Suicidal Ideation Attributes Scale, or any combinations thereof.

In some embodiments, at least one sign or symptom of depression is alleviated within 24 hours of administration of the psilocybin. In some embodiments, at least one symptom of depression is alleviated within 1 week of administration of the psilocybin. In some embodiments, at least one symptom of depression is alleviated for a period of at least 1 month after administration of the psilocybin. In some embodiments, at least one symptom of depression is alleviated for a period of at least 3 months after administration of the psilocybin. In some embodiments, at least one symptom of depression is alleviated for a period of at least 12 months after administration of the psilocybin.

In some embodiments, no other treatment is administered to the subject to reduce the sign or symptom of depression after administration of the psilocybin.

In some embodiments, the method of the present disclosure further comprises administering to the subject at least one additional therapeutic to reduce the sign or symptom of depression. In some embodiments, at least one additional therapeutic is a selective serotonin reuptake inhibitor, a serotonin and norepinephrine reuptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, a dopamine reuptake inhibitor, a 5-HT1A receptor antagonist, a 5-HT2 receptor antagonist, a 5-HT3 receptor antagonist, a monoamine oxidase inhibitor, or a noradrenergic antagonist. In some embodiments, at least one additional therapeutic is administered prior to administration of psilocybin, on the same day as the administration of psilocybin, or after administration of psilocybin.

In some embodiments, the subject with the depressive disorder has an additional comorbidity or disorder. In some embodiments, the additional comorbidity or disorder is an anxiety disorder, an obsessive-compulsive disorder, alcoholism, a personality disorder, a cardiovascular

disease, a neurological disease, or cancer. In some embodiments, the subject has dementia, Alzheimer's Disease, or Parkinson's Disease. In some embodiments, reducing at least one sign or symptom of depression in the subject using the methods of the present disclosure prevents one or more comorbidities or disorders in the subject.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin or a metabolite thereof, wherein the subject has one or more of the following diseases, disorders, or conditions: Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment-Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum Depression, Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches (including Chronic Cluster Headaches), Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, or Kleptomania.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeuticallyeffective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: a Neurocognitive Disorder due to Alzheimer's, Lewy Bodies, Traumatic Brain Injury, Prion Disease, HIV Infection, Parkinson's, Huntington's; concussion; Chronic Traumatic Encephalopathy (CTE); Language Disorder, Speech Sound Disorder (Phonological Disorder);

Childhood-Onset Fluency Disorder (Stuttering); Social (Pragmatic) Communication Disorder; Tourette's Disorder; Persistent (Chronic) Motor or Vocal Tic Disorder; Amnestic Disorder Due to Known Physiological Condition (possibly in electroconvulsive therapy (ECT) resistant subjects); Transient Cerebral Ischemic Attack, Cerebral Infarction, Cerebral Bleeding, Progressive Supranuclear Ophthalmoplegia; or Retrograde Amnesia.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Autism Spectrum Disorder, or Antisocial Personality Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Attention-Deficit/Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder or Unspecified Attention-Deficit/Hyperactivity Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Schizotypal (Personality) Disorder, Delusional Disorder, Schizophrenia, or Schizoaffective Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions selected from Insomnia Disorder, Hypersomnolence Disorder, Narcolepsy, or Primary Central Sleep Apnea.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Schizoid Personality Disorder, Schizotypal Personality Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, or Obsessive-Compulsive Personality Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Female Sexual Interest/Arousal Disorder, Male Hypoactive Sexual Desire Disorder, or Excessive Sexual Drive.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: from Bipolar I Disorder, Bipolar II Disorder, or Cyclothymic Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Age-Related Hearing Loss or Tinnitus.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Multiple Sclerosis, Cranial Nerve Disorder, Neuromyelitis Optica, Bell's Palsy, Guillain Barre Syndrome, Demyelinating Disease of Central Nervous System, or Chronic Inflammatory Demyelinating Polyneuritis.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective dose of psilocybin, wherein the subject suffers from pain, such as phantom pain, chronic pain, or pain associated with another disease or disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has one or more of the following diseases, disorders, or conditions: Myelopathy, Traumatic Brain Injury, Intellectual Disabilities, Mania, Neurodegeneration, Paraphilic disorders (e.g, Pedophilic Disorder), Suicidal Behavior Disorder, Nonsuicidal Self-Injury, Persistent Complex Bereavement Disorder, Gastrointestinal Tract Related Diseases (e.g., Irritable Bowel Syndrome (IBS)), Epilepsy, Sickle Cell Disease, Locked-in Syndrome, Restless Leg Syndrome, Stroke (such as ischemic stroke or hemorrhagic stroke), or Amyotrophic Lateral Sclerosis (ALS).

In some embodiments, the disclosure provides a method of treating a subject, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein, after administration, the subject exhibits an improvement in cognition. In some embodiments, the improvement in cognition is an improvement in attention, episodic memory, working memory, spatial memory, social cognition, executive function, and/or cognitive flexibility.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Treatment-Resistant Depression (TRD).

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Major Depressive Disorder (MDD)

In some embodiments, the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin comprises at least 90% by weight of Polymorph A. In some embodiments, the crystalline psilocybin comprises at least 95% by weight of Polymorph A. In some embodiments, the crystalline psilocybin has a chemical purity of greater than 97% by high performance liquid chromatography (HPLC), and no single impurity of greater than 1%.

In some embodiments the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%. In some embodiments the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns and the second variant has a particle size of about 90 to 150 microns. In some embodiments, 30% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 70% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns. In some embodiments the psilocybin is administered in an oral dosage form. In some embodiments the psilocybin is administered in a capsule. In some embodiments the psilocybin is administered in a tablet.

In some embodiments, at least one dose of psilocybin is administered to the subject. In some embodiments, the dose of psilocybin is in the range of about 0.1 mg to about 100 mg. In some embodiments, the dose of psilocybin is about 25 mg.

In some embodiments, the subject participates in at least one psychological support session before administration of the psilocybin. In some embodiments, the subject participates in at least one psychological support session after administration of the psilocybin. In some embodiments, a therapist provides psychological support to the subject for approximately 4-8 hours after administration of the psilocybin.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a numbered structural formula of psilocybin.

FIG. 2a is a XRPD diffractogram of Polymorph A (GM764B).

FIG. 2b is a XRPD diffractogram of Polymorph A' (JCCA2160F).

FIG. 2c is a XRPD diffractogram of Polymorph B (JCCA2160-F-TM2).

FIG. 2d is a XRPD diffractogram of a Hydrate A (JCCA2157E).

FIG. 2e is a XRPD diffractogram of an ethanol solvate (JCCA2158D).

FIG. 2f is a XRPD diffractogram of product obtained during development of the process (CB646-E) (top) - compared to the diffractograms Polymorph A' (JCCA2160F) (middle) and Polymorph B (JCCA2160-TM2) (bottom).

FIG. 3a is a DSC and TGA thermograph of Polymorph A (GM764B).

FIG. 3b is a DSC and TGA thermograph of Polymorph A' (JCCA2160F).

FIG. 3c is a DSC thermograph of Polymorph B (GM748A).

FIG. 3d is a DSC and TGA thermograph of Hydrate A (JCCA2157E).

FIG. 3e is a DSC and TGA thermograph of ethanol solvate (JCCA2158D).

FIG. 4 is a form phase diagram showing the inter-relationship of form in water-based systems.

FIG. 5 is a 1H NMR (Nuclear Magnetic Resonance) spectrum of psilocybin.

FIG. 6 is a 13C NMR spectrum of psilocybin.

FIG. 7 is a FT-IR Spectrum of psilocybin.

FIG. 8 is a Mass Spectrum of psilocybin.

Fig. 9A shows a timeline of the Phase 1 exploratory study, which evaluated psilocybin treatment in healthy volunteer subjects.

Fig. 9B shows the number of subjects that completed screening (Visit 1), baseline measurements (Visit 2), and drug administration (Visit 3) of the Phase 1 exploratory study.

Fig. 9C shows the group sizes of the dosing sessions of the Phase 1 exploratory study.

Fig. 9D shows the most frequently reported adverse events of the Phase 1 exploratory study.

Fig. 9E shows the duration of adverse events of the Phase 1 exploratory study.

Fig. 9F shows a graph of the Paired Associates Learning Total Errors Adjusted (PALTEA) score of the Cambridge Neuropsychological Test Automated Battery (CANTAB) over time for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9G shows a graph of the least squares mean difference from placebo for the PALTEA score of the CANTAB over time for the psilocybin-treated subjects of the Phase 1 exploratory study.

Fig. 9H shows a graph of the spatial working memory between errors (SWMBE) score of the CANTAB over time for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9I shows a graph of the least squares mean difference from placebo for the SWMBE score of the CANTAB over time for the psilocybin-treated subjects of the Phase 1 exploratory study.

Fig. 9J shows a graph of the spatial working memory strategy (SWM strategy) score of the CANTAB over time for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9K shows a graph of the least squares mean difference from placebo for the SWM strategy score of the CANTAB over time for the psilocybin-treated subjects of the Phase 1 exploratory study.

Fig. 9L shows a graph of the Rapid Visual Information Processing A Prime (RVPA) score of the CANTAB over time for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9M shows a graph of the least squares (LS) mean difference of psilocybin groups (10 mg and 25 mg) compared to placebo groups over time. Psilocybin was administered on Day 0. Data on Days 7 and Day 28 were collected remotely. Positive scores indicate psilocybin performed better than placebo. Negative scores indicate placebo performed better than psilocybin. LS means were calculated using repated-measures ANOVA and compared with placebo. $^{*}p \leq 0.05$. Data are expressed as LS mean ± sem.

Fig. 9N shows a graph of the Emotional Recognition Task percent correct (ERTPC) of the CANTAB for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 90 shows a graph of the One Touch Stockings Problems Solved on First Choice (OTSPSFC) of the CANTAB for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9P shows a graph of the intra-extra dimensional set shift total errors (IEDYERT) of the CANTAB for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9Q shows a graph of the CANTAB global composite score over time for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9R shows a graph of the least squares mean difference from placebo for the CANTAB global composite score over time for the psilocybin-treated subjects of the Phase 1 exploratory study.

Fig. 9S shows a graph of the verbal fluency test for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9T shows a graph of the digit span forward test for the psilocybin-treated and placebo-treated subjects of the Phase 1 exploratory study.

Fig. 9U shows a graph of the Five Dimensional - Altered States of Consciousness (5D-ASC), which measures alterations in mood, perception, and experience of self, after administration of psilocybin or placebo in the Phase 1 exploratory study.

Fig. 9V shows the difference in CANTAB composite score between “psilocybin-naive” (0, left-hand side) subjects and subjects with prior psilocybin experience (1, right-hand side).

Fig. 10A shows the study design of the clinical trial examining psilocybin in major depressive disorder.

Fig. 10B shows the study timeline for examining psilocybin in major depressive disorder.

Fig. 10C shows a timeline of the first dosing session (Visit 3) in the clinical study.

Fig. 11 shows the study design of the clinical trial examining psilocybin in treatment resistant depression.

Fig. 12 shows the study design of the clinical trial examining psilocybin in bipolar disorder.

Fig. 13A is a graph showing the changes in amount of wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep over 24 hours in a rat Wistar-Kyoto model of TRD following psilocybin administration. Black arrow denotes dosing time. Grey background denotes dark period (awake period in rodents).

Fig. 13E is a graph showing the changes in the absolute and relative wakefulness, NREM and REM sleep EEG power with frequency in a rat Wistar-Kyoto model of TRD.

Fig. 13B is a graph showing the amount of wakefulness, NREM sleep and REM sleep 1-7 hours (light period, sleep period in rodents) post-dosing with psilocybin in a rat Wistar-Kyoto model of treatment-resistant depression. Statistical analysis by repeated measures ANOVA followed by Dunnett post-hoc test, $^{*}p<0.05$.

Fig. 13C is a graph showing the amount of wakefulness, NREM sleep and REM sleep 11-19 hours (dark period, awake period in rodents) post-dosing with psilocybin in a rat Wistar-Kyoto model of treatment-resistant depression. Statistical analysis by repeated measures ANOVA followed by Dunnett post-hoc test, $^{*}p<0.05$.

Fig. 13D is a graph showing the changes in the absolute and relative wakefulness electroencephalogram (EEG) power with frequency, and the amount of gamma oscillations in a rat Wistar-Kyoto model of treatment-resistant depression. Statistical analysis by repeated measures ANOVA followed by Dunnett post-hoc test, $^{*}p<0.05$.

DETAILED DESCRIPTION

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the detailed description herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

The singular forms “a,” “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Furthermore, the term “about” as used herein when referring to a measurable value such as a dose, time, temperature, and the like, is meant to encompass variations of ± 20%, ± 10%, ± 5%, ± 1%, ± 0.5%, or even ± 0.1% of the specified amount.

The phrase “and/or,” as used herein in the specification and in the embodiments, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements can optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only

(optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the embodiments, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of' or "exactly one of," or, when used in the embodiments, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the embodiments, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the embodiments, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements can optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

Unless the context indicates otherwise, it is specifically intended that the various features described herein can be used in any combination.

As used herein, the terms "reduce," "decrease," "lessen" and similar terms mean a decrease of at least about 10%, about 15%, about 20%, about 25%, about 35%, about 50%, about 75%, about 80%, about 85%, about 90%, about 95%, about 97%, or more.

As used herein, the terms “improve,” “increase,” “enhance,” and similar terms indicate an increase of at least about 10%, about 15%, about 20%, about 25%, about 50%, about 75%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more.

Reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. When a range of values is expressed, another embodiment includes from the one particular value and/or to the other particular value. Further, reference to values stated in ranges include each and every value within that range. All ranges are inclusive and combinable.

As used herein, “substantially absent” with reference to XRPD diffractogram peak means the peak has a relative intensity compared to a reference peak present in the diffractogram of less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% of the intensity of the reference peak, or that the peak is not detectable.

XRPD diffractograms and XRPD peak positions may be acquired using Cu Ka radiation.

DSC thermograms and TGA thermograms may be acquired using a heating rate of 20°C/min.

As used herein, the term “diffusion tensor imaging” or “DTI” refers to a technique that detects how water travels along the white matter tracts in the brain. In some embodiments, DTI is used to characterize microstructural changes associated with mental disorders (e.g., major depressive disorder) and/or the response to treatment in subjects with mental disorders.

All disease and disorders listed herein are defined as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association, or in International Classification of Diseases (ICD), published by the World Health Organization.

As used herein the term “subject” and “patient” are used interchangeably.

As used herein, “treating” and like terms refer to reducing the severity and/or frequency of one or more symptoms, eliminating one or more symptoms and/or the underlying cause of said symptoms, reducing the frequency or likelihood of one or more symptoms and/or their underlying cause, delaying, preventing and/or slowing the progression of diseases and/or disorders and improving or remediating damage caused, directly or indirectly, by the diseases and/or disorders.

As used herein, “therapeutically-effective dose” means a dose sufficient to achieve the intended therapeutic purpose, such as, to alleviate a sign or symptom of a disease or disorder in a subject.

As used herein a “precursor” and/or “derivative” of psilocybin includes, but is not limited to, prodrugs of psilocybin, prodrugs of an active metabolite of psilocybin, and an active metabolite of psilocybin.

As used herein, a subject that is “psilocybin-naive” has not previously been exposed to psilocybin.

As used herein, the following Medical Dictionary for Regulatory Activities (MedDRA) terms are considered to be adverse events that are psychedelic in nature: altered mood, altered state of consciousness, autoscopy, delusional perception, disinhibition, dissociation, dissociative identity disorder, dreamy state, emotional disorder, euphoric mood, feeling abnormal, hallucination, hyperacusis, hyperaesthesia, hypoaesthesia, illusion, paranoia, parosmia, photophobia, sensory disturbance, time perception altered, thinking abnormal, synaesthesia, substance-induced psychotic distress, and somatic hallucination.

Depressive Disorders

In some embodiments, the methods provided herein are used to treat a subject with a depressive disorder. As used herein, the terms “depressive disorder”, “depression disorder”, or “depression” refers to a group of disorders characterized by low mood that can affect a person’s thoughts, behavior, feelings, and sense of well-being lasting for a period of time. In some embodiments, the depressive disorder disrupts the physical and psychological functions of a person. In some embodiments, the depressive disorder causes a physical symptom such as weight loss, aches or pains, headaches, cramps, or digestive problems. In some embodiments, the depressive disorder causes a psychological symptom such as persistent sadness, anxiety, feelings of hopelessness and irritability, feelings of guilt, worthlessness, or helplessness, loss of interest or pleasure in hobbies and activities, difficulty concentrating, remembering, or making decisions.

In some embodiments, the depressive disorder is major depressive disorder, atypical depression, bipolar disorder, catatonic depression, depressive disorder due to a medical condition, postpartum depression, premenstrual dysphoric disorder, or seasonal affective disorder.

As used herein, the term “major depressive disorder” refers to a condition characterized by a time period of low mood that is present across most situations. Major depressive disorder is often accompanied by low self-esteem, loss of interest in normally enjoyable activities, low energy, and pain without a clear cause. In some instances, major depressive order is characterized by two weeks. In some instances, an individual experiences periods of depression separated by years. In some instances, an individual experiences symptoms of depression that

are nearly always present. Major depressive disorder can negatively affect a person's personal, work, or school life, as well as sleeping, eating habits, and general health. Approximately 2-7% of adults with major depressive disorder commit suicide, and up to 60% of people who commit suicide had major depressive disorder or another related mood disorder. Dysthymia is a subtype of major depressive disorder consisting of the same cognitive and physical problems as major depressive disorder with less severe but longer-lasting symptoms. Exemplary symptoms of a major depressive disorder include, but are not limited to, feelings of sadness, tearfulness, emptiness or hopelessness, angry outbursts, irritability or frustration, even over small matters, loss of interest or pleasure in most or all normal activities, sleep disturbances, including insomnia or sleeping too much, tiredness and lack of energy, reduced appetite, weight loss or gain, anxiety, agitation or restlessness, slowed thinking, speaking, or body movements, feelings of worthlessness or guilt, fixating on past failures or self-blame, trouble thinking, concentrating, making decisions, and remembering things, frequent thoughts of death, suicidal thoughts, suicide attempts, or suicide, and unexplained physical problems, such as back pain or headaches.

As used herein, the term "atypical depression" refers to a condition wherein an individual shows signs of mood reactivity (i.e., mood brightens in response to actual or potential positive events), significant weight gain, increase in appetite, hypersomnia, heavy, leaden feelings in arms or legs, and/or long-standing pattern of interpersonal rejection sensitivity that results in significant social or occupational impairment. Exemplary symptoms of atypical depression include, but are not limited to, daily sadness or depressed mood, loss of enjoyment in things that were once pleasurable, major changes in weight (gain or loss) or appetite, insomnia or excessive sleep almost every day, a state of physical restlessness or being rundown that is noticeable by others, daily fatigue or loss of energy, feelings of hopelessness, worthlessness, or excessive guilt almost every day, problems with concentration or making decisions almost every day, recurring thoughts of death or suicide, suicide plan, or suicide attempt.

As used herein, the term "bipolar disorder" refers to a condition that causes an individual to experience unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. Individuals with bipolar disorder experience periods of unusually intense emotion, changes in sleep patterns and activity levels, and unusual behaviors. These distinct periods are called "mood episodes." Mood episodes are drastically different from the moods and behaviors that are typical for the person. Exemplary symptoms of mania, excessive behavior, include, but are not limited to, abnormally upbeat, jumpy, or wired behavior; increased activity, energy, or agitation, exaggerated sense of well-being and self-confidence, decreased need for sleep, unusual talkativeness, racing thoughts, distractibility, and poor decision-making—for example,

going on buying sprees, taking sexual risks, or making foolish investments. Exemplary symptoms of depressive episodes or low mood, include, but are not limited to, depressed mood, such as feelings of sadness, emptiness, hopelessness, or tearfulness; marked loss of interest or feeling no pleasure in all—or almost all—activities, significant weight loss, weight gain, or decrease or increase in appetite, insomnia or hypersomnia (excessive sleeping or excessive sleepiness), restlessness or slowed behavior, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, decreased ability to think or concentrate, or indecisiveness, and thinking about, planning or attempting suicide.

Bipolar disorder includes bipolar I disorder, bipolar II disorder, and cyclothymic disorder. Bipolar I disorder is defined by manic episodes that last at least 7 days or by severe manic symptoms that require hospitalization. A subject with bipolar I disorder may also experience depressive episodes typically lasting at least 2 weeks. Episodes of depression with mixed features, i.e. depressive and manic symptoms at the same time, are also possible. Bipolar II disorder is characterized by a pattern of depressive and hypomanic episodes, but not severe manic episodes typical of bipolar I disorder. Cyclothymic disorder (also referred to as cyclothymia) is characterized by periods of hypomanic symptoms (elevated mood and euphoria) and depressive symptoms lasting over a period of at least 2 years. The mood fluctuations are not sufficient in number, severity, or duration to meet the full criteria for a hypomanic or depressive episode.

As used herein, the term “catatonic depression” refers to a condition causing an individual to remain speechless and motionless for an extended period. Exemplary symptoms of catatonic depression include, but are not limited to, feelings of sadness, which can occur daily, a loss of interest in most activities, sudden weight gain or loss, a change in appetite, trouble falling asleep, trouble getting out of bed, feelings of restlessness, irritability, feelings of worthlessness, feelings of guilt, fatigue, difficulty concentrating, difficulty thinking, difficulty making decisions, thoughts of suicide or death, and/or a suicide attempt.

As used herein, the term “depressive disorder due to a medical condition” refers to a condition wherein an individual experiences depressive symptoms caused by another illness. Examples of medical conditions known to cause a depressive disorder include, but are not limited to, HIV/AIDS, diabetes, arthritis, strokes, brain disorders such as Parkinson’s disease, Huntington’s disease, multiple sclerosis, and Alzheimer’s disease, metabolic conditions (e.g. vitamin B12 deficiency), autoimmune conditions (e.g., lupus and rheumatoid arthritis), viral or other infections (hepatitis, mononucleosis, herpes), back pain, and certain cancers (e.g., pancreatic).

As used herein, the term “postpartum depression” refers to a condition as the result of childbirth and hormonal changes, psychological adjustment to parenthood, and/or fatigue. Postpartum depression is often associated with women, but men can also suffer from postpartum depression as well. Exemplary symptoms of postpartum depression include, but are not limited to, feelings of sadness, hopeless, emptiness, or overwhelmed; crying more often than usual or for no apparent reason; worrying or feeling overly anxious; feeling moody, irritable, or restless; oversleeping, or being unable to sleep even when the baby is asleep; having trouble concentrating, remembering details, and making decisions; experiencing anger or rage; losing interest in activities that are usually enjoyable; suffering from physical aches and pains, including frequent headaches, stomach problems, and muscle pain; eating too little or too much; withdrawing from or avoiding friends and family; having trouble bonding or forming an emotional attachment with the baby; persistently doubting his or ability to care for the baby; and thinking about harming themselves or the baby.

As used herein, the term “premenstrual dysphoric disorder” refers to a condition wherein an individual expresses mood lability, irritability, dysphoria, and anxiety symptoms that occur repeatedly during the premenstrual phase of the cycle and remit around the onset of menses or shortly thereafter. Exemplary symptoms of premenstrual dysphoric disorder includes, but are not limited to, lability (e.g., mood swings), irritability or anger, depressed mood, anxiety and tension, decreased interest in usual activities, difficulty in concentration, lethargy and lack of energy, change in appetite (e.g., overeating or specific food cravings), hypersomnia or insomnia, feeling overwhelmed or out of control, physical symptoms (e.g., breast tenderness or swelling, joint or muscle pain, a sensation of ‘bloating’ and weight gain), self-deprecating thoughts, feelings of being keyed up or on edge, decreased interest in usual activities (e.g., work, school, friends, hobbies), subjective difficulty in concentration, and easy fatigability.

As used herein, the term “seasonal affective disorder” refers to a condition wherein an individual experiences mood changes based on the time of the year. In some instances, an individual experiences low mood, low energy, or other depressive symptoms during the fall and/or winter season. In some instances, an individual experiences low mood, low energy, or other depressive symptoms during the spring and/or summer season. Exemplary symptoms of seasonal affective disorder include, but are not limited to, feeling depressed most of the day or nearly every day, losing interest in activities once found enjoyable, having low energy, having problems with sleeping, experiencing changes in appetite or weight, feeling sluggish or agitated, having difficulty concentrating, feeling hopeless, worthless, or guilty, and having frequent thoughts of death or suicide.

In some embodiments, a depressive disorder comprises a medical diagnosis based on the criteria and classification from Diagnostic and Statistical Manual of Medical Disorders, 5th Ed. In some embodiments, a depressive disorder comprises a medical diagnosis based on an independent medical evaluation.

In some embodiments, the methods described herein are provided to a subject with depression that is resistant to treatment. In some embodiments, the subject has been diagnosed with "treatment-resistant depression". The term "treatment-resistant depression" refers to a kind of depression that does not respond or is resistant to at least one or more treatment attempts of adequate dose and duration. In some embodiments, the subject with treatment-resistant depression has failed to respond to 1 treatment attempt, 2 treatment attempts, 3 treatment attempts, 4 treatment attempts, or 5 treatment attempts. In some embodiments, the subject with treatment-resistant depression has been diagnosed with major depressive disorder and has failed to respond to 3 or more treatment attempts. In some embodiments, the subject with treatment-resistant depression has been diagnosed with bipolar disorder and has failed to respond to 1 treatment attempt.

In some embodiments, the methods provided herein reduce at least one sign or symptom of a depressive disorder. In some embodiments, the methods provided herein reduce at least one sign or symptom of a depressive disorder by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of major depressive disorder. In some embodiments, the methods provided herein reduce at least one sign or symptom of major depressive disorder by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of atypical depression. In some embodiments, the methods provided herein reduce at least one sign or symptom of atypical depression by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about

80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of bipolar disorder. In some embodiments, the methods provided herein reduce at least one sign or symptom of bipolar disorder by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of bipolar I disorder. In some embodiments, the methods provided herein reduce at least one sign or symptom of bipolar I disorder by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of bipolar II disorder. In some embodiments, the methods provided herein reduce at least one sign or symptom of bipolar II disorder by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of catatonic depression. In some embodiments, the methods provided herein reduce at least one sign or symptom of catatonic depression by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of a depressive disorder due to a medical condition. In some embodiments, the methods provided herein reduce at least one sign or symptom of a depressive disorder due to a medical condition by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %,

about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of postpartum depression. In some embodiments, the methods provided herein reduce at least one sign or symptom of postpartum depression by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of premenstrual dysphoric disorder. In some embodiments, the methods provided herein reduce at least one sign or symptom of premenstrual dysphoric disorder by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the methods provided herein reduce at least one sign or symptom of seasonal affective disorder. In some embodiments, the methods provided herein reduce at least one sign or symptom of seasonal affective disorder by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression is reduced or eliminated in the subject within 1 hour, 2 hours, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, 3 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, or 3 months following administration of psilocybin or an active metabolite thereof.

In some embodiments, the sign or symptom of depression is reduced or eliminated in the subject for a period of 1 day, 3 days, 7 days, 10 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 18 months, 24 months, or 48 months following administration of psilocybin or an active metabolite thereof. In some embodiments, there is no recurrence of depression in the subject upon administration of psilocybin or an active metabolite thereof.

In some embodiments, no other treatment is administered to the subject to reduce the sign or symptom of depression after administration of the psilocybin.

In some embodiments, the method of the present disclosure further comprises administering to the subject at least one additional therapeutic to reduce the sign or symptom of depression. In some embodiments, at least one additional therapeutic is a selective serotonin reuptake inhibitor, a serotonin and norepinephrine reuptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, a dopamine reuptake inhibitor, a 5-HT1A receptor antagonist, a 5-HT2 receptor antagonist, a 5-HT3 receptor antagonist, a monoamine oxidase inhibitor, or a noradrenergic antagonist. In some embodiments, at least one additional therapeutic is administered prior to administration of psilocybin, on the same day as the administration of psilocybin, or after administration of psilocybin.

In some embodiments, the subject with the depressive disorder has an additional comorbidity or disorder. In some embodiments, the additional comorbidity or disorder is an anxiety disorder, an obsessive-compulsive disorder, alcoholism, a personality disorder, a cardiovascular disease, a neurological disease, or cancer. In some embodiments, the subject has dementia, Alzheimer's Disease, or Parkinson's Disease. In some embodiments, reducing at least one sign or symptom of depression in the subject using the methods of the present disclosure prevents one or more comorbidities or disorders in the subject.

Psilocybin

In some embodiments, a method of treatment comprises the administration of a therapeutically effective amount of psilocybin, a prodrug of psilocybin, an active metabolite of psilocybin, or a prodrug of an active metabolite of psilocybin to a subject in need thereof as described herein. In some embodiments, a method of treatment comprises the administration of a therapeutically effective amount of psilocybin as described herein. In some embodiments, a method of treatment comprises the administration of a therapeutically effective amount of psilocin as described herein. Some embodiments comprise psilocybin, a prodrug of psilocybin, an active metabolite of psilocybin, or a prodrug of an active metabolite of psilocybin for use in the treatment of an indication as described herein. Some embodiments comprise psilocybin for use in the treatment of an indication as described herein. Some embodiments comprise psilocin for use in the treatment of an indication as described herein. Some embodiments comprise the use of psilocybin, a prodrug of psilocybin, an active metabolite of psilocybin, or a prodrug of an active metabolite of psilocybin in the manufacture of a medicament for the treatment of an indication as described herein.

A numbered structural formula of psilocybin is shown in Fig. 1. Novel polymorphs and hydrates of psilocybin, along with the preparation and formulations thereof are disclosed in U.S Application No. US201 9/01 19310 A 1, which is incorporated by reference herein in its entirety. US2019/01 19310 discloses a number of formulations and the challenges of formulating psilocybin due to e.g. its hygroscopicity and poor flow characteristics. US2019/01 19310 also discloses the importance of a controlled aqueous crystallisation process.

In some embodiments, the psilocybin comprises crystalline psilocybin in the form Polymorph A or Polymorph A', as described herein, the crystalline psilocybin exhibiting peaks in an X-ray powder diffraction (XRPD) diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ. In some embodiments, the crystalline psilocybin further exhibits at least one peak in the XRPD diffractogram at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ. Illustrative XRPD diffractograms are provided as FIGs. 2A and 2B. In some embodiments, the crystalline psilocybin exhibits an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C. Illustrative DSC thermograms are provided as FIGs. 3A and 3B.

Polymorph A

In some embodiments, the present disclosure provides crystalline psilocybin in the form Polymorph A, characterized by one or more of:

- peaks in an XRPD diffractogram at 11.5, 12.0,14.5, and 17.5, °2Θ±0.1 °2Θ;
- peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5, °2Θ±0.1 °2Θ, further characterized by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ;
- an XRPD diffractogram as substantially illustrated in FIG. 2a; or
- an endothermic event in a DSC thermogram having an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in FIG. 3a.

In some embodiments, the peak at 17.5 °2Θ±0.1 °2Θ has a relative intensity compared to the peak at 14.5 °2Θ±0.1 °2Θ of at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, or at least 10%.

In some embodiments, the present disclosure provides crystalline psilocybin in the form Polymorph A, characterized by one or more of:

- peaks in an XRPD diffractogram at 11.5, 12.0,14.5, and 17.5, °2Θ±0.2°2Θ;

- peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5, °2Θ±0.2°2Θ, further characterized by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.2°2Θ;
- an XRPD diffractogram as substantially illustrated in FIG. 2a; or
- « an endothermic event in a DSC thermogram having an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in FIG. 3a.

In some embodiments, the crystalline psilocybin of Polymorph A exhibits an XRPD diffractogram having at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 of the peaks listed in Table A, or equivalent peaks within about ±0.1 °2θ of the peaks listed in Table A. In some embodiments, the crystalline psilocybin of Polymorph A exhibits an XRPD diffractogram having at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 of the peaks listed in Table A, or equivalent peaks within about ±0.2°20 of the peaks listed in Table A. In some embodiments, Polymorph A exhibits a peak at 17.5 °2Θ±0.1 °2Θ that is substantially absent in Polymorph A'. In some embodiments, Polymorph A exhibits a peak at 17.5 °2Θ±0.2°2Θ that is substantially absent in Polymorph A'.

Table A - XRPD peak positions for Polymorph A

Position [°2Th.]	Relative Intensity [%]
5.6	8.42
11.5	13.05
12.0	26.45
14.5	100.00
17.5	10.71
19.7	37.29
20.4	20.06
22.2	17.83
23.2	6.99
24.3	17.93
25.7	16.40
26.8	3.15
27.8	4.54
29.7	9.53
31.2	6.51
32.6	2.45
33.7	1.75

In some embodiments, crystalline psilocybin Polymorph A exhibits XRPD diffractogram peaks at 11.5, 12.0, 14.5, and 17.5°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph A exhibits at least one additional peak appearing at 19.7, 20.4, 22.2, 24.3 or 25.7°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph A exhibits at least two additional peaks appearing at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph A exhibits at least three additional peaks appearing at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph A exhibits an XRPD diffractogram substantially the same as the XRPD diffractogram shown in FIG. 2A.

In some embodiments, crystalline psilocybin Polymorph A is characterized by XRPD diffractogram peaks at 14.5 and 17.5°2Θ±0.1 °2Θ with the peak at 17.5°20 having an intensity which is at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, or at least about 10% of the intensity of the peak at 14.5°20.

In some embodiments, the crystalline psilocybin Polymorph A exhibits no peak at 10.1 — that is, the peak at 10.1 is absent or substantially absent.

In some embodiments, crystalline psilocybin Polymorph A is characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C such as between 145 and 160°C, or such as between 145 and 155°C and a second onset temperature of between 205 and 220°C, such as between 210 and 220°C, such as between 210 and 218°C, or such as between 210 and 216°C. In some embodiments, crystalline psilocybin Polymorph A exhibits an endothermic event in a DSC thermogram having an onset temperature of between about 205 and about 220°C, between about 210 and about 220°C, between about 210 and about 218°C, or between about 210 and about 216°C. In some embodiments, crystalline psilocybin Polymorph A further exhibits an endothermic event in the DSC thermogram having an onset temperature of between about 145 and about 165°C, between about 145 and about 160°C, or between about 145 and about 155°C. In some embodiments, crystalline psilocybin Polymorph A exhibits an endothermic event having an onset temperature of between about 205 and about 220°C, between about 210 and about 220°C, between about 210 and about 218°C, or between about 210 and about 216°C; and an endothermic event having an onset temperature of between about 145 and about 165°C, between about 145 and about 160°C, between about 145 and about 155°C, in a DSC thermogram. In some embodiments, crystalline psilocybin Polymorph A exhibits a DSC thermogram substantially the same as the DSC thermogram in FIG. 3A.

In some embodiments, crystalline psilocybin Polymorph A exhibits a water content of <0.5% w/w, <0.4% w/w, <0.3% w/w, <0.2% w/w, or <0.1% w/w. The water content of a crystalline compound can be determined by known methods, for example Karl Fischer Titration. In some

embodiments, crystalline psilocybin Polymorph A exhibits <0.5% w/w loss, <0.4% w/w, <0.3% w/w, <0.2% w/w, or <0.1% w/w in the TGA thermogram between ambient temperature, e.g., about 25°C, and 200°C. In some embodiments, crystalline psilocybin Polymorph A loses less than 2% by weight, less than 1% by weight, or than 0.5% by weight in a loss on drying test, e.g., a loss on drying test performed at 70°C.

In some embodiments, crystalline psilocybin Polymorph A is a highly pure crystalline form of Polymorph A, for example, the in a loss on drying test psilocybin comprises at least 90%, at least 95%, at least 99%, or at least 99.5% by weight crystalline psilocybin of Polymorph A.

In some embodiments, crystalline psilocybin Polymorph A is a white to off-white solid.

In some embodiments, crystalline psilocybin Polymorph A is chemically pure, for example the psilocybin has a chemical purity of greater than 97%, 98%, or 99% by HPLC. In some embodiments, crystalline psilocybin Polymorph A has no single impurity of greater than 1%, greater than 0.5%, greater than 0.4%, greater than 0.3%, or greater than 0.2% e.g., the impurity phosphoric acid as measured by ^{31}P NMR, or the impurity psilocin measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A has a chemical purity of greater than 97 area%, greater than 98 area%, or greater than 99 area% by HPLC. In some embodiments, crystalline psilocybin Polymorph A has no single impurity greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A does not contain psilocin at a level greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A does not contain phosphoric acid at a level greater than 1 weight%, greater than 0.5 weight%, greater than 0.4 weight%, 0.3 weight%, or greater than 0.2 weight%, as measured by ^{31}P NMR. In some embodiments, crystalline psilocybin Polymorph A has a chemical assay of at least 95 weight%, at least 96 weight%, or at least 98 weight%.

Methods of Manufacturing Crystalline Psilocybin Polymorph A.

In another embodiment, the disclosure provides a method for large scale manufacture of psilocybin characterized in that the method comprises subjecting psilocybin to a water crystallization step, with controlled drying, to produce crystalline psilocybin Polymorph A.

In another embodiment, the disclosure provides a method for large scale manufacture of psilocybin characterized in that the method comprises subjecting psilocybin to a water crystallization step, with controlled drying, to produced crystalline psilocybin Polymorph A with an XRPD diffractogram as illustrated in Fig 2a and a DSC and TGA thermograph as illustrated in Fig 3a. In another embodiment, the disclosure provides a method for large-scale manufacture of

psilocybin characterized in that the method comprises subjecting psilocybin to a water crystallization step, with controlled drying, to produce a high purity crystalline psilocybin - Polymorph A with an XRPD diffractogram as illustrated in Fig 2a and a DSC thermograph as illustrated in Fig 3a.

In another embodiment of the disclosure, psilocybin is recrystallized in about 10-20 volumes of water, heated with agitation to a temperature of at least 70°C, polish filtered with a suitable cut off (typically, below 5 pm), seeded at a temperature of about 70°C, and cooled in a controlled manner to about 5°C over a period of more than 2 hours.

In some embodiments, psilocybin recrystallization comprises controlled cooling which drops the temperature by about 5 °C -15 °C an hour, more preferably about 10°C an hour. In certain embodiments, the polish filter step is done through an appropriately sized filter such as, but not limited to, a 1.2pm in line filter.

In some embodiments, agitation is by stirring at about 400-500 rpm, typically about 450 rpm.

In some embodiments, the psilocybin is dissolved in water heated to no more than 90°C. In some embodiments the psilocybin is dissolved in water heated to no more than 85°C. Without being bound by any particular mechanism, this dissolution step is intended to solubilize psilocybin whilst also minimizing the formation of hydrolysis products.

In some embodiments, the psilocybin solution is stirred to speed the solubilization and reduce the time that the solution is at a high temperature, namely one at or around 80°C, or higher.

In some embodiments, the seed is psilocybin Hydrate A. In one embodiment, 0.1% weight or less of seed is added to the process.

In some embodiments, the psilocybin the crystalline psilocybin is isolated by vacuum filtration.

In some embodiments, the isolated crystals are dried in vacuo at a temperature of at least 30°C, such as between 30 and 50°C, or such as between 40 and 50°C. In some embodiment, the isolated crystals are dried in vacuo for at least 10 hours, such as between 12 and 18 hours, or such as about 30 hours. In some embodiments, the isolated crystals are dried in vacuo at a temperature of at least 30°C, such as between 30 and 50°C, or such as between 40 and 50°C, for at least 10 hours, such as between 12 and 18 hours, or such as about 30 hours. In some embodiments, the isolated crystals are dried until the isolated crystals lose less than 2% weight in a loss on drying test, such as less than 0.5% weight.

In some embodiments, the isolated crystals are washed, several times, in water and dried in vacuo at about 50°C for at least 12 hours.

In some embodiments, the crystals obtained are typically relatively large (range 50 to 200 microns) and uniform when viewed under the microscope x 10.

In contrast, crystals obtained without controlled cooling which are much smaller in size (typically 5 to 50microns) when viewed under the microscope x 10.

In some embodiments, there is provided Psilocybin obtained by the method of crystallization described herein.

In some embodiments, there is provided a pharmaceutical formulation comprising psilocybin polymorph A obtained by the method of crystallization described herein.

In some embodiments, psilocybin manufactured prior to crystallization may be produced using one of the following methods: synthetic or biological, e.g. by fermentation or obtained by extraction from mushrooms. In some embodiments, psilocybin manufactured prior to crystallization is manufactured according to all or some of the methods described in U.S Application No. US201 9/01 19310 A 1, which is incorporated by reference herein in its entirety.

Polymorph A'

The present disclosure provides crystalline psilocybin in the form of Polymorph A', characterized by one or more of:

(i) peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °2Θ±0.1 °2Θ;

(ii) peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °2Θ±0.1 °2Θ, further characterized by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ;

(iii) an XRPD diffractogram as substantially illustrated in Figure 2b; or

(iv) an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in Figure 3b.

In some embodiments, the crystalline psilocybin comprises crystalline psilocybin Polymorph A'. Crystalline psilocybin Polymorph A' exhibits peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1°2Θ, but absent or substantially absent of a peak at 17.5 °2Θ±0.1°2Θ. In some embodiments, crystalline psilocybin Polymorph A' further exhibits 1, 2, 3, 4, or 5 peaks selected from 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ. An illustrative XRPD diffractogram for Polymorph A' is provided as FIG. 2B. An illustrative DSC thermogram having an onset temperature of between 205 and 220°C for Polymorph A' is provided as FIG. 3B.

In some embodiments, psilocybin Polymorph A' exhibits an XRPD diffractogram as summarized in Table B. In some embodiments, crystalline psilocybin Polymorph A' exhibits at

least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or25 peaks listed of Table B or equivalent peaks within about ±0.1 °2θ, and absent or substantially absent peak at 17.5 °2Θ±0.1°2Θ.

Table B - XRPD peak positions for Polymorph A'

Position [°2Th.]	Relative Intensity [%]
5.5	4.89
10.1	4.09
11.5	22.05
12.0	22.77
14.5	100.00
14.9	11.29
17.5	1.08
18.7	2.44
19.4	23.02
19.6	33.70
20.3	17.01
21.1	12.08
21.6	8.51
22.2	15.54
22.6	8.78
23.1	10.11
24.3	21.83
25.1	4.36
25.8	15.40
26.3	4.28
26.8	2.86
27.8	5.96
28.6	1.91
29.7	10.56
31.1	7.35
32.6	3.72
33.8	1.54

In some embodiments, crystalline psilocybin Polymorph A' exhibits XRPD diffractogram peaks at 11.5, 12.0, and 14.5°2Θ±0.1 °2Θ but substantially absent of a peak at 17.5 °2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph A' further exhibits at least one additional peak appearing at 19.7, 20.4, 22.2, 24.3, or 25.7 °2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph A' exhibits at least two additional peaks appearing at 19.7, 20.4, 22.2, 24.3, or 25.7 °2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph A' exhibits and is

distinguished from Polymorph A by the presence of a peak appearing at 10.1 °2Θ±0.1 °2Θ. In yet a further embodiment, crystalline psilocybin Polymorph A' exhibits an XRPD diffractogram substantially the same as the XRPD diffractogram shown in FIG. 2B.

In some embodiments, crystalline psilocybin Polymorph A' exhibits XRPD diffractogram peaks at 14.5 and 17.5°2Θ±0.1 °2Θ, wherein the intensity of the peak at 17.5°20 is less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% of the intensity of the peak at 14.5°20.

In some embodiments, crystalline psilocybin Polymorph A' exhibits XRPD diffractogram peaks at 10.1 and 14.5°2Θ±0.1 °2Θ, wherein the intensity of the peak at 10.1°20 is at least 1%, at least 2%, at least 3%, or at least 4% of the intensity of the peak at 14.5°20.

In some embodiments, crystalline psilocybin Polymorph A' is characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C such as between 145 and 160°C, or such as between 145 and 155°C and a second onset temperature of between 205 and 220°C, such as between 210 and 220°C, such as between 210 and 218°C, or such as between 210 and 216°C. In some embodiments, crystalline psilocybin Polymorph A' is characterized by an endothermic event in a DSC thermogram having an onset temperature of between about 205 and about 220°C, between about 210 and about 220°C, between about 210 and about 218°C, or between about 210 and about 216°C. In some embodiments, crystalline psilocybin Polymorph A' exhibits an endothermic event in the DSC thermogram having an onset temperature of between about 145 and about 165°C, between about 145 and about 160°C, or between about 145 and about 155°C. In some embodiments, crystalline psilocybin Polymorph A' exhibits an endothermic event having an onset temperature of between about 205 and about 220°C, between about 210 and about 220°C, between about 210 and about 218°C, or between about 210 and about 216°C, and an endothermic event having an onset temperature of between about 145 and about 165°C, between about 145 and about 160°C, or between about 145 and about 155°C, in a DSC thermogram. In some embodiments, crystalline psilocybin Polymorph A' exhibits a DSC thermogram substantially the same as the DSC thermogram in FIG. 3B.

In some embodiments, crystalline psilocybin Polymorph A' exhibits a water content of <0.5% w/w, <0.4% w/w, <0.3% w/w, <0.2% w/w, or <0.1% w/w. Methods to determine the water content of a crystalline compound are known, for example Karl Fischer Titration. In some embodiments, crystalline psilocybin Polymorph A' exhibits <0.5% w/w loss, <0.4% w/w, <0.3% w/w, <0.2% w/w, <0.1% w/w in the TGA thermogram between ambient temperature, e.g., 25°C, and 200°C. In some embodiments, crystalline psilocybin Polymorph A' loses less than 2% by

weight, less than 1% by weight, or less than 0.5% by weight in a loss on drying test. In some embodiments, the loss on drying test is performed at 70°C.

In some embodiments, crystalline psilocybin Polymorph A' is a highly pure crystalline form of Polymorph A'. In some embodiments, the crystalline psilocybin comprises at least 90%, 95%, 99%, or 99.5% by weight of Polymorph A'.

In some embodiments, crystalline psilocybin Polymorph A's is a white to off white solid.

In some embodiments, crystalline psilocybin Polymorph A' is chemically pure, for example the psilocybin has a chemical purity of greater than 97%, greaterthan 98%, orthan 99% by HPLC. In some embodiments, crystalline psilocybin Polymorph A' has no single impurity of greater than 1% or greater than 0.5%, e.g., the impurity phosphoric acid as measured by ^{31}P NMR or the impurity psilocin as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A' has a chemical purity of greater than 97 area%, greater than 98 area%, or greater than 99 area% by HPLC. In some embodiments, crystalline psilocybin Polymorph A' has no single impurity greater than 1 area% or greater than 0.5 area%, e.g., as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A' does not contain psilocin at a level greaterthan 1 area% or greater than 0.5 area% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A' does not contain phosphoric acid at a level greater than 1 weight% or greaterthan 0.5 weight% as measured by ^{31}P NMR. In some embodiments, crystalline psilocybin Polymorph A' has a chemical assay of at least 95 weight%, at least 96 weight%, or at least 98 weight%.

In some embodiments, crystalline psilocybin Polymorph A' is chemically pure, for example the psilocybin has a chemical purity of greater than 97%, 98%, or 99% by HPLC. In some embodiments, crystalline psilocybin Polymorph A' has no single impurity of greater than 1%, greater than 0.5%, greater than 0.4%, greater than 0.3%, or greater than 0.2% e.g., the impurity phosphoric acid as measured by ^{31}P NMR, or the impurity psilocin measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A' has a chemical purity of greaterthan 97 area%, greater than 98 area%, or greater than 99 area% by HPLC. In some embodiments, crystalline psilocybin Polymorph A' has no single impurity greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A' does not contain psilocin at a level greaterthan 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A' does not contain phosphoric acid at a level greater than 1 weight%, greater than 0.5 weight%, greater than 0.4 weight%, 0.3 weight%, or greater than 0.2 weight%, as measured by ^{31}P NMR. In some

embodiments, crystalline psilocybin Polymorph A' has a chemical assay of at least 95 weight%, at least 96 weight%, or at least 98 weight%.

Illustrative XRPD diffractograms for high purity crystalline psilocybin, Polymorph A or Polymorph A' are provided in FIGs. 2A and 2B. Illustrative DSC thermographs for high purity crystalline psilocybin, Polymorph A or Polymorph A' are provided in FIGs. 2A and 2B.

Polymorph A (including its isostructural variant Polymorph A') (FIGs. 2A and 2B) differs from Polymorph B (FIG. 2C), the Hydrate A (FIG. 2D) and the ethanol solvate (FIG. 2E: Solvate A), and the relationship between some of the different forms is illustrated in FIG. 4.

In some embodiments, the crystalline psilocybin Polymorph A or Polymorph A' is a white to off white solid, and/or has a chemical purity of greater than 97%, 98%, or 99% by HPLC. In some embodiments, crystalline psilocybin Polymorph A or Polymorph A' has no single impurity of greater than 1%, greater than 0.5%, greater than 0.4%, greater than 0.3%, or greater than 0.2% e.g., the impurity phosphoric acid as measured by ^{31}P NMR, or the impurity psilocin measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A or Polymorph A' has a chemical purity of greater than 97 area%, greater than 98 area%, or greater than 99 area% by HPLC. In some embodiments, crystalline psilocybin Polymorph A or Polymorph A' has no single impurity greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A or Polymorph A' does not contain psilocin at a level greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph A or Polymorph A' does not contain phosphoric acid at a level greater than 1 weight%, greater than 0.5 weight%, greater than 0.4 weight%, 0.3 weight%, or greater than 0.2 weight%, as measured by ^{31}P NMR. In some embodiments, crystalline psilocybin Polymorph A or Polymorph A' has a chemical assay of at least 95 weight%, at least 96 weight%, or at least 98 weight%.

The heating of Polymorph A or A' results in an endothermic event having an onset temperature of circa 150°C corresponding to solid-solid transition of Polymorph A or Polymorph A' to Polymorph B. Continued heating of the resulting solid, i.e., Polymorph B, results in a second endothermic event corresponding to a melting point having an onset temperature of between 205 and 220°C (see FIGs. 3A and 3B).

Hydrate A

In some embodiments, the disclosure provides a crystalline form of psilocybin, Hydrate A. In some embodiments, crystalline psilocybin Hydrate A exhibits peaks in an XRPD diffractogram at 8.9, 12.6 and 13.8°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Hydrate A further

exhibits at least 1, 2, 3, 4, or 5 further peaks at 6.5, 12.2, 19.4, 20.4 or 20.8°2Θ±0.1 °2Θ. An illustrative XRPD diffractogram is provided as FIG. 2D. In some embodiments, crystalline psilocybin Hydrate A further exhibits an endothermic event in a DSC thermogram having a first onset temperature of between 90°C and 100°C, a second onset temperature of between 100°C and 120°C and a third onset temperature of between 210°C and 220°C. An illustrative DSC thermogram is provided as FIG. 2D.

In some embodiments, psilocybin Hydrate A exhibits an XRPD diffractogram comprising at least 3, 4, 5, 6, 7, 8, 9, or 10 peaks listed in Table C or equivalent peaks within about ±0.1 °2θ.

Table C: XRPD peak positions for Hydrate A

Position [°2Th.]	Relative Intensity [%]
5.6	14.40
6.5	18.84
8.9	100.00
12.2	11.51
12.6	18.65
13.8	44.22
16.2	21.22
18.9	6.62
19.4	38.68
20.4	21.32
20.8	19.73
21.5	20.75
22.3	12.80
22.5	19.38
23.1	47.53
23.5	25.79
24.3	5.62
24.8	14.62
25.4	5.27
26.9	6.53
27.9	7.82
28.4	5.78
29.0	5.09
29.7	4.83
32.1	8.27
32.8	4.81
33.4	3.74

Position [°2Th.]	Relative Intensity [%]
34.2	5.96

In some embodiments, crystalline psilocybin Hydrate A exhibits XRPD diffractogram peaks at 8.9, 12.6 and 13.8°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Hydrate A exhibits at least one peak appearing at 6.5, 12.2, 19.4, 20.4 or 20.8°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Hydrate A exhibits at least two peaks appearing at 6.5, 12.2, 19.4, 20.4 or 20.8°20±0. 1°2θ. In some embodiments, crystalline psilocybin Hydrate A exhibits an XRPD diffractogram substantially the same as the XRPD diffractogram shown in FIG. 2D.

In certain embodiments, crystalline psilocybin Hydrate A is characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 85°C and 105°C, such as between 90°C and 100°C and most preferably at about 96°C, a second onset temperature of between 100°C and 120°C such as between 105°C and 115°C, and most preferably at about 109°C and a third onset temperature of between 205 and 220°C, such as between 210 and 220°C, such as between 210 and 218°C, or such as between 210 and 216°C, or about 216°C. In some embodiments, crystalline psilocybin Hydrate A exhibits an endothermic event in a DSC thermogram having an onset temperature of between about 205 and about 220°C, between about 210 and about 220°C, between about 210 and about 218°C, or between about 210 and about 216°C. In some embodiments, crystalline psilocybin Hydrate A exhibits an endothermic event in the DSC thermogram having an onset temperature of between about 85 and about 105°C, or between about 90 and about 100°C. In some embodiments, crystalline psilocybin Hydrate A exhibits an endothermic event having an onset temperature of between about 205 and about 220°C, between about 210 and about 220°C, between about 210 and about 218°C, or between about 210 and about 216°C, and an endothermic event having an onset temperature of between about 85 and about 105°C or between about 90 and about 100°C, in a DSC thermogram. In some embodiments, crystalline psilocybin Hydrate A exhibits a DSC thermogram substantially the same as the DSC thermogram in FIG. 3D.

In some embodiments, crystalline psilocybin Hydrate A exhibits a water content of between about 10 and about 18%, between about 12 and about 16%, or about 13%. Methods to determine the water content of a crystalline compound are known, for example Karl Fischer Titration. In some embodiments, crystalline psilocybin Hydrate A exhibits a weight loss in the TGA thermogram of between about 10 and about 18%, between about 12 and about 16%, or about 13%, between ambient temperature, about 25°C, and 120°C.

In some embodiments, crystalline psilocybin Hydrate A is chemically pure, for example the psilocybin has a chemical purity of greater than 97%, 98%, or 99% by HPLC. In some embodiments, crystalline psilocybin Hydrate A has no single impurity of greater than 1%, greater than 0.5%, greater than 0.4%, greater than 0.3%, or greater than 0.2% e.g., the impurity phosphoric acid as measured by ^{31}P NMR, or the impurity psilocin measured by HPLC. In some embodiments, crystalline psilocybin Hydrate A has a chemical purity of greater than 97 area%, greater than 98 area%, or greater than 99 area% by HPLC. In some embodiments, crystalline psilocybin Hydrate A has no single impurity greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Hydrate A does not contain psilocin at a level greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Hydrate A does not contain phosphoric acid at a level greater than 1 weight%, greater than 0.5 weight%, greater than 0.4 weight%, 0.3 weight%, or greater than 0.2 weight%, as measured by ^{31}P NMR. In some embodiments, crystalline psilocybin Hydrate A has a chemical assay of at least 95 weight%, at least 96 weight%, or at least 98 weight%.

In some embodiments, crystalline psilocybin Hydrate A is a highly pure crystalline form of Hydrate A. In some embodiments, the crystalline psilocybin comprises at least 90%, at least 95%, at least 99%, or at least 99.5% by weight of Hydrate A.

Polymorph B

In some embodiments, the disclosure provides a crystalline form of psilocybin, Polymorph B. In some embodiments, crystalline psilocybin Polymorph B exhibits peaks in an XRPD diffractogram at 11.1, 11.8 and 14.3°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph B exhibits at least 1, 2, 3, 4 or 5 peaks in an XRPD diffractogram at 14.9, 15.4, 19.3, 20.0 or 20.6°2θ±0.1 °2θ. An illustrative XRPD diffractogram of crystalline psilocybin Polymorph B is provided as FIG. 2C. In some embodiments, crystalline psilocybin Polymorph B exhibits a single endothermic event in a DSC thermogram having an onset temperature of between about 205 and about 220°C. An illustrative DSC thermogram of crystalline psilocybin Polymorph B is provided as FIG. 3C.

In some embodiments, psilocybin Polymorph B exhibits an XRPD diffractogram comprising at least 3, 4, 5, 6, 7, 8, 9, or 10 peaks listed in Table D or equivalent peaks within about ±0.1 °2θ.

Table D: XRPD peak positions for Polymorph B

Position [°2Th.]	Relative Intensity [%]
5.5	21.33
11.1	36.91
11.8	100.00
12.5	12.73
14.3	70.23
14.9	50.01
15.4	23.67
17.1	51.58
17.4	91.25
18.0	12.61
19.3	39.33
20.0	76.61
20.6	50.26
21.5	20.77
22.3	40.19
23.9	13.32
24.3	16.03
25.3	32.94
28.3	7.60
28.9	17.89
29.3	8.96
31.3	6.57
32.2	6.90
33.8	2.37

In some embodiments, crystalline psilocybin Polymorph B exhibits XRPD diffractogram peaks at 11.1, 11.8 and 14.3°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph B exhibits at least one peak at 14.9, 15.4, 19.3, 20.0 or 20.6°2Θ±0.1°2Θ. In some embodiments, crystalline psilocybin Polymorph B exhibits at least two peaks appearing at 14.9, 15.4, 19.3, 20.0 or 20.6°2Θ±0.1 °2Θ. In some embodiments, crystalline psilocybin Polymorph B exhibits an XRPD diffractogram substantially the same as the XRPD diffractogram shown in FIG. 2C.

In some embodiments, crystalline psilocybin Polymorph B is characterized by a single endothermic event in a DSC thermogram having an onset temperature of between about 205 and about 220°C, between about 210 and about 220°C, between about 210 and about 218°C, or

between about 210 and about 216°C. In some embodiments, crystalline psilocybin Polymorph B exhibits a DSC thermogram substantially the same as the DSC thermogram in FIG. 3C.

In some embodiments, crystalline psilocybin Polymorph B exhibits a water content of <0.5% w/w, <0.4% w/w, <0.3% w/w, <0.2% w/w, or <0.1% w/w. Methods to determine the water content of a crystalline compound are known, for example Karl Fischer Titration. In some embodiments, crystalline psilocybin Polymorph B exhibits <0.5% w/w, <0.4% w/w, <0.3% w/w, <0.2% w/w, or <0.1% w/w loss in the TGA thermogram between ambient temperature, about 25°C, and 200°C. In some embodiments, crystalline psilocybin Polymorph B exhibits a loss of less than 2% by weight, less than 1% by weight, or less than 0.5% by weight in a loss on drying test. In some embodiments, the loss on drying test is performed at 70°C.

In some embodiments, crystalline psilocybin Polymorph B is a highly pure crystalline form of Polymorph B, for example, psilocybin comprises at least 90%, at least 95%, at least 99%, or at least 99.5% by weight of Polymorph B.

In some embodiments, crystalline psilocybin Polymorph B is chemically pure, for example the psilocybin has a chemical purity of greater than 97%, 98%, or 99% by HPLC. In some embodiments, crystalline psilocybin Polymorph B has no single impurity of greater than 1%, greater than 0.5%, greater than 0.4%, greater than 0.3%, or greater than 0.2% e.g., the impurity phosphoric acid as measured by ^{31}P NMR, or the impurity psilocin measured by HPLC. In some embodiments, crystalline psilocybin Polymorph B has a chemical purity of greater than 97 area%, greater than 98 area%, or greater than 99 area% by HPLC. In some embodiments, crystalline psilocybin Polymorph B has no single impurity greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph B does not contain psilocin at a level greater than 1 area%, greater than 0.5 area%, greater than 0.4%, greater than 0.3%, or greater than 0.2% as measured by HPLC. In some embodiments, crystalline psilocybin Polymorph B does not contain phosphoric acid at a level greater than 1 weight%, greater than 0.5 weight%, greater than 0.4 weight%, 0.3 weight%, or greater than 0.2 weight%, as measured by ^{31}P NMR. In some embodiments, crystalline psilocybin Polymorph B has a chemical assay of at least 95 weight%, at least 96 weight%, or at least 98 weight%.

In some embodiments, the psilocybin of the disclosure in the form Polymorph A or A' has the general properties illustrated in Table D.

Table D

Appearance:	White to off-white solid
Major endothermic event in DSC (onset temperature) (corresponding to a melt):	210-215°C
Hygroscopicity:	Psilocybin forms Hydrate A at high humidity and when added to water but the water of hydration is lost rapidly on drying. The anhydrous form is therefore being developed.
Crystalline form:	Anhydrous Polymorph A and/ or A'
pKa (calculated):	1.74, 6.71, 9.75
Solubility	*approx.* 15 mg/ml in Water

In some embodiments, the psilocybin conforms to the spectra as set out in Table E and illustrated in the spectra of FIGs. 5-8.

Table E

Technique	Conclusions
Proton (^{1}H) and Carbon (^{13}C) NMR	Assignment of the proton (FIG. 5) and carbon spectra (FIG. 6) are concordant with Psilocybin.
FT-Infrared Spectroscopy (FT-IR)	Assignment of the FT-IR spectrum (FIG. 7) is concordant with Psilocybin.
Mass Spectroscopy (MS)	Assignment of the mass spectrum (FIG. 8) is concordant with Psilocybin.

Alternatively, and independently, the crystalline psilocybin may take the form of Hydrate A or Polymorph B.

In some embodiments, the disclosure provides the crystalline psilocybin in the form Polymorph A or Polymorph A' for use in medicine. In some embodiments, the disclosure provides crystalline psilocybin Polymorph A for use in medicine. In some embodiments, the disclosure provides crystalline psilocybin Polymorph A' for use in medicine. In some embodiments, the disclosure provides a high purity crystalline psilocybin Polymorph A for use in medicine. In some embodiments, the disclosure provides a high purity crystalline psilocybin Polymorph A' for use in medicine. Alternatively, and independently, the crystalline psilocybin may take the form of Hydrate A or Polymorph B.

In some embodiments, the disclosure provides crystalline psilocybin in the form Polymorph A or Polymorph A' for use in treating a subject in need thereof. Alternatively, and independently, the crystalline psilocybin may take the form of Hydrate A or Polymorph B.

In some embodiments, the disclosure provides crystalline psilocybin, Polymorph A or Polymorph A', for use in treating a subject in need thereof. In some embodiments, the disclosure provides crystalline psilocybin, Polymorph A or Polymorph A', for use in treating a subject in need thereof. In some embodiments, the disclosure provides crystalline psilocybin Polymorph A for use in treating a subject in need thereof. In some embodiments, the disclosure provides crystalline psilocybin Polymorph A' for use in treating a subject in need thereof. In some embodiments, the disclosure provides a high purity crystalline psilocybin Polymorph A for use in treating a subject in need thereof. In some embodiments, the disclosure provides a high purity crystalline psilocybin Polymorph A' for use in treating a subject in need thereof.

Pharmaceutical Compositions and Formulations

In some embodiments, the disclosure provides a pharmaceutical composition comprising crystalline psilocybin and one or more pharmaceutically acceptable carriers or excipients.

In some embodiments, the disclosure provides a pharmaceutical formulation comprising high purity psilocybin and one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the disclosure provides a pharmaceutical formulation comprising crystalline psilocybin Polymorph A and one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the disclosure provides a pharmaceutical formulation comprising crystalline psilocybin Polymorph A' and one or more pharmaceutically carriers or excipients. In some embodiments, the disclosure provides a pharmaceutical formulation comprising high purity crystalline psilocybin, Polymorph A or Polymorph A', and one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the disclosure provides a pharmaceutical formulation comprising high purity crystalline psilocybin Polymorph A and one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the disclosure provides a pharmaceutical formulation comprising high purity crystalline psilocybin Polymorph A' and one or more pharmaceutically acceptable carriers or excipients.

Preferred pharmaceutical excipients for an oral formulation include: diluents, such as microcrystalline cellulose, starch, mannitol, calcium hydrogen phosphate anhydrous or co-mixtures of silicon dioxide, calcium carbonate, microcrystalline cellulose and talc; disintegrants, such as sodium starch glycolate or croscarmellose sodium; binders, such as povidone, co-povidone or hydroxyl propyl cellulose; lubricants, such as magnesium stearate or sodium stearyl fumurate; glidants, such as colloidal silicon dioxide; and film coats, such as Opadry II white or PVA based brown Opadry II.

In some embodiments, the oral dosage form also comprises a disintegrant, such as, but not limited to: starch glycolate, croscarmellose sodium, and/or mixtures thereof. In some

embodiments, the oral dosage form comprises 3% or less by wt disintegrant, less than 3% by wt disintegrant and greater than 0.001% by wt disintegrant, about 2.5% by wt or less disintegrant; 2% by wt or less disintegrant; 1.5% by wt or less disintegrant; 1% by wt or less disintegrant; 0.7% by wt or less disintegrant; 0.5% by wt or less disintegrant, or 0.3% by wt or less disintegrant.

In some embodiments, the disintegrant is sodium starch glycolate. In some embodiments, the sodium starch glycolate is present at less than 3% wt. In Other embodiments, the sodium starch glycolate is present at about 2% by wt or less, about 2% by wt; about 1% by wt or less, about 1% by wt; about 0.7% by wt or less, about 0.7% by wt; about 0.5% by wt or less, or about 0.5% by wt.. In still other embodiments, the sodium starch glycolate is present at about 0.5% to 1% by wt.

In some embodiments, the oral dosage form comprises 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%. In some embodiments, the oral dosage form comprises 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%. In some embodiments, the oral dosage form comprises 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

In some embodiments, the oral dosage form comprises 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%. In some embodiments, the oral dosage form comprises 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%. In some embodiments, the oral dosage form comprises 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

In some embodiments, the oral dosage form comprises 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%. In some embodiments, the oral dosage form comprises 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%. In some embodiments, the oral dosage form comprises 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

In some embodiments there is provided the crystalline psilocybin in the form Polymorph A or Polymorph A' for use in medicine. In some embodiments, there is provided crystalline psilocybin Polymorph A for use in medicine. In some embodiments, there is provided crystalline

psilocybin Polymorph A' for use in medicine. In some embodiments, there is provided a high purity crystalline psilocybin Polymorph A for use in medicine. In some embodiments, there is provided a high purity crystalline psilocybin Polymorph A' for use in medicine.

Alternatively, and independently, the crystalline psilocybin may take the form of Hydrate A or Polymorph B.

In some embodiments, there is provided crystalline psilocybin, particularly but not essentially in the form Polymorph A or Polymorph A' for use in treating central nervous disorders.

Alternatively, and independently, the crystalline psilocybin may take the form of Hydrate A or Polymorph B.

In some embodiments, the pharmaceutical formulation is a parenteral dosage form. In some embodiments, the pharmaceutical formulation is an oral dosage form. In some embodiments, the pharmaceutical composition comprises a tablet. In some embodiments, the pharmaceutical composition comprises a capsule. In some embodiments, the pharmaceutical composition comprises a dry powder. In some embodiments, the pharmaceutical composition comprises a solution. In some embodiments, more than one dosage form is administered to the subject at substantially the same time. In some embodiments, the subject may be administered the entire therapeutic dose in one tablet or capsule. In some embodiments, the therapeutic dose may be split among multiple tablets or capsules. For example, for a dose of 25 mg, the subject may be administered 5 tablets or capsules each comprising 25 mg of psilocybin. Alternatively, for a dose of 10 mg, the subject may be administered 2 tablets or capsules each comprising 5 mg of psilocybin.

In some embodiments, the oral dosage form comprises a functional filler. The functional filler may be a silicified filler, such as, but not limited to silicified microcrystalline cellulose (SMCC). In some embodiments, the oral dosage form comprises high compactability grades of SMCC with a particle size range of from about 45 to 150 microns. A mixture of two functional fillers having different particle size ranges may be used with the weight percentages of the two favoring the larger sized particles.

In some embodiments, the silicified microcrystalline filler may comprise a first filler, having a particle size range of from about 45 to 80 microns in an amount of up to 30%, up to 20%, up to 15%, or less by weight of filler, and a second filler, having a particle size range of from about 90 to 150 microns, in an amount of up to 70%, up to 80%, up to 85%, or more, by weight of filler.

In some embodiments, the oral dosage form may comprise silicified microcrystalline cellulose with a particle size range of from about 45 to 80 microns (SMCC 50), such as Prosolv 50; silicified microcrystalline cellulose with a particle size range of from about 90 to 150 microns

(SMCC 90), such as Prosolv 90; or mixtures thereof. In other embodiments, the oral dosage form may comprise SMCC 50 and SMCC 90. In other embodiments, the oral dosage form may comprise SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:5 to 1:8 wt%. In still other embodiments the ratio of SMCC 50 to SMCC 90 is 1:5-1 :7; 1:6-1 :7; 1:6-1 :8; or 1.7-1.8. In still other embodiments the ratio of SMCC 50 to SMCC 90 is 1:6; 1:6.1 ; 1:6.2; 1:6.3; 1:6.4; 1:6.5; 1:6.6; 1.6.7; 1:6.8; 1.6.9; or 1:7. The formulation may further comprise or consist essentially of a disintegrant, including without limitation sodium starch glycolate; a glidant, including without limitation colloidal silicon dioxide; and a lubricant, including without limitation sodium stearyl fumarate.

In some embodiments, the oral dosage form may comprise a disintegrant such as sodium starch glycolate, at less than 3% (by wt), less than 2%, or 1% or less.

In some embodiments, the oral dosage form comprises 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%. In some embodiments, the oral dosage form comprises 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%. In some embodiments, the oral dosage form comprises 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

In some embodiments, the oral dosage form comprises 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%. In some embodiments, the oral dosage form comprises 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%. In some embodiments, the oral dosage form comprises 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

In some embodiments, the oral dosage form comprises 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%. In some embodiments, the oral dosage form comprises 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%. In some embodiments, the oral dosage form comprises 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

In some embodiments, the oral dosage form comprises 5 mg of crystalline psilocybin in the form of Polymorph A, 12.5 mg of SMCC 50, 79.5 mg of SMCC 90, 1 mg sodium starch

glycolate, 1 mg colloidal silicon dioxide and 1 mg sodium stearyl fumarate. In some embodiments, the tablet or capsule comprises 5 mg of crystalline psilocybin in the form of Polymorph A, 12.5 mg of SMCC 50, 79.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide and 1 mg sodium stearyl fumarate.

In some embodiments, the oral dosage form comprises 1 mg of crystalline psilocybin in the form of Polymorph A, 20.5 mg of SMCC 50, 75.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide, and 1 mg sodium stearyl fumarate. In some embodiments, the tablet or capsule comprises 1 mg of crystalline psilocybin in the form of Polymorph A, 20.5 mg of SMCC 50, 75.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide, and 1 mg sodium stearyl fumarate.

In some embodiments, the tablet or capsule comprises one or more excipients. Non-limiting exemplary excipients include microcrystalline cellulose and starch, including without limitation silicified microcrystalline cellulose.

It should be noted that the formulations may comprise psilocybin in any form, not only the polymorphic forms disclosed herein.

As used herein, oral doses of psilocybin are classified follows: “very low doses” (about 0.045 mg/kg or less); “low doses” (between about 0.1 15 and about 0.125 mg/kg), “medium doses” (between about 0.1 15 to about 0.260 mg/kg), and “high doses” (about 0.315 mg/kg or more). See Studerus et al (201 1) *J Psychopharmacol* 25(1 1) 1434-1452.

In some embodiments, the formulated dose of psilocybin comprises from about 0.01 mg/kg to about 1 mg/kg. In some embodiments, a human dose (for an adult weighing 60-80kg) comprises between about 0.60 mg and about 80 mg.

In some embodiments, a formulated dose comprises between about 2 and about 50 mg of crystalline psilocybin. In some embodiments, a formulated dose comprises between 2 and 40 mg, between 2 and 10 mg, between 5 and 30 mg, between 5 and 15 mg, or between 20 and 30 mg of crystalline psilocybin. In some embodiments, a formulated dose comprises about 1 mg, about 5 mg, about 10 mg, or about 25 mg of crystalline psilocybin.

In some embodiments, a formulated dose comprises between about 2 and about 50 mg of crystalline psilocybin Polymorph A or Polymorph A’ or a mixture thereof. In some embodiments, a formulated dose comprises between 2 and 40 mg, between 2 and 10 mg, between 5 and 30 mg, between 5 and 15 mg, or between 20 and 30 mg of crystalline psilocybin Polymorph A or Polymorph A’ or a mixture thereof. In some embodiments, a formulated dose comprises about 1 mg, about 5 mg, about 10 mg, or about 25 mg of crystalline psilocybin Polymorph A or Polymorph

A' or a mixture thereof. In some embodiments, a formulated dose comprises about 5 mg of crystalline psilocybin Polymorph A or Polymorph A' or a mixture thereof.

In some embodiments, a formulated dose comprises between about 2 and about 50 mg of crystalline psilocybin Polymorph A. In some embodiments, a formulated dose comprises between 2 and 40 mg, between 2 and 10 mg, between 5 and 30 mg, between 5 and 15 mg, or between 20 and 30 mg of crystalline psilocybin Polymorph A. In some embodiments, a formulated dose comprises about 1 mg, about 5 mg, about 10 mg, or about 25 mg of crystalline psilocybin Polymorph A.

In some embodiments, a formulated dose comprises between about 2 and about 50 mg of crystalline psilocybin Polymorph A'. In some embodiments, a formulated dose comprises between 2 and 40 mg, between 2 and 10 mg, between 5 and 30 mg, between 5 and 15 mg, or between 20 and 30 mg of crystalline psilocybin Polymorph A'. In some embodiments, a formulated dose comprises about 1 mg, about 5 mg, about 10 mg, or about 25 mg of crystalline psilocybin Polymorph A'.

In some embodiments, a formulated dose comprises between about 2 and about 50 mg of crystalline psilocybin Polymorph B. In some embodiments, a formulated dose comprises between 2 and 40 mg, between 2 and 10 mg, between 5 and 30 mg, between 5 and 15 mg, or between 20 and 30 mg of crystalline psilocybin Polymorph B. In some embodiments, a formulated dose comprises about 1 mg, about 5 mg, about 10 mg, or about 25 mg of crystalline psilocybin Polymorph B.

In some embodiments, a formulated dose comprises between about 2 and about 50 mg of crystalline psilocybin Hydrate A. In some embodiments, a formulated dose comprises between 2 and 40 mg, between 2 and 10 mg, between 5 and 30 mg, between 5 and 15 mg, or between 20 and 30 mg of crystalline psilocybin Hydrate A. In some embodiments, a formulated dose comprises about 1 mg, about 5 mg, about 10 mg, or about 25 mg of crystalline psilocybin Hydrate A.

Dosing

In some embodiments, a therapeutically effective dose of psilocybin is administered to the subject. In some embodiments, each dose of psilocybin administered to the subject is a therapeutically effective dose.

In some embodiments, a dose of psilocybin may be in the range of about 1 mg to about 100 mg. For example, the dose may be about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg,

about 90 mg, about 95 mg, or about 100 mg. In some embodiments, the dose of psilocybin is between about 0.1 mg to about 100 mg, about 1 mg to about 50 mg, or about 5 mg to about 30 mg. In some embodiments, the dose of psilocybin is about 1 mg, about 10 mg, or about 25 mg. In some embodiments, the dose of psilocybin is in the range of about 0.001 mg to about 1 mg. In some embodiments, the dose of psilocybin is in the rage of about 100 mg to about 250 mg. In some embodiments, the dose of psilocybin is about 25 mg. In some embodiments, the psilocybin is in the form of polymorph A.

In some embodiments, an adult oral dose comprises about 1 mg to about 40 mg, about 2 to about 30 mg, or about 15 to about 30 mg of crystalline psilocybin, for example about 1 mg, about 5 mg, about 10 mg, or about 25 mg of crystalline psilocybin. In some embodiments, an adult oral dose comprises about 25 mg of crystalline psilocybin. In some embodiments, the crystalline psilocybin is in the form of polymorph A.

In some embodiments, a "micro-dose" of psilocybin is administered to a subject. A micro-dose may comprise, for example, about 0.05 mg to about 2.5 mg of crystalline psilocybin, such as about 1.0 mg. In the case of micro-dosing the regime may comprise a regular, continuous regime of, for example, daily administration, every other day administration, or weekly, administration. Such dosing may be absent of psychological support.

In some embodiments, one dose of psilocybin is administered to the subject. In some embodiments, multiple doses of psilocybin are administered to the subject. For example, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 50 doses of psilocybin may be administered to the subject. In some embodiments, the same dose of psilocybin is administered to a subject during each administration. In some embodiments, a different dose of psilocybin is administered to a subject during each administration. In some embodiments, the dose of psilocybin administered to the subject is increased over time. In some embodiments, the dose of psilocybin administered to the subject is decreased over time.

In some embodiments, the psilocybin is administered at therapeutically effective intervals. In some embodiments, a therapeutically effective interval may be about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, or about 12 weeks. In some embodiments, a therapeutically effective interval may be about 1 month, about 3 months, about 6 months, or about 12 months. In some embodiments, the psilocybin is administered once per day. In some embodiments, the psilocybin is administered at least once per week or at least twice per week. In some embodiments, the psilocybin is administered at least once per month or at least twice per month.

In some embodiments, the psilocybin is administered at least once every three months, at least once every six months, or at least once every 12 months.

In some embodiments, a first dose and a second dose of psilocybin are administered to the subject. In some embodiments, the first dose is about 1 mg and the second dose is about 1 mg. In some embodiments, the first dose is about 10 mg and the second dose is about 10 mg. In some embodiments, the first dose is about 25 mg and the second dose is about 25 mg. In some embodiments, the first dose is about 10 mg and the second dose is about 25 mg. In some embodiments, the first dose is about 25 mg and the second dose is about 10 mg. In some embodiments, the first dose is about 1 mg and the second dose is about 10 mg. In some embodiments, the first dose is about 1 mg and the second dose is about 25 mg. In some embodiments, the first dose is about 10 mg and the second dose is about 1 mg. In some embodiments, the first dose is about 25 mg and the second dose is about 1 mg.

In some embodiments a second dose of psilocybin is administered from about one week to about 12 weeks after a first dose. In some embodiments, a second dose of psilocybin is administered about one week after a first dose. In some embodiments, a second dose of psilocybin is administered about two weeks after a first dose. In some embodiments, a second dose of psilocybin is administered about three weeks after a first dose. In some embodiments, a second dose of psilocybin is administered about four weeks after a first dose. In some embodiments, a second dose of psilocybin is administered about five weeks after a first dose. In some embodiments, a second dose of psilocybin is administered about six weeks after a first dose.

Administration Routes

Exemplary modes for administration of psilocybin include oral, parenteral (e.g., intravenous, subcutaneous, intradermal, intramuscular [including administration to skeletal, diaphragm and/or cardiac muscle], intradermal, intrapleural, intracerebral, and intra-articular), topical *(e.g.,* to both skin and mucosal surfaces, including airway surfaces, and transdermal administration), inhalation *(e.g.,* via an aerosol), rectal *(e.g.,* via a suppository), transmucosal, intranasal, buccal *(e.g.,* sublingual), vaginal, intrathecal, intraocular, transdermal, in utero (or *in ovo),* intralymphatic, and direct tissue or organ injection *(e.g.,* to liver, skeletal muscle, cardiac muscle, diaphragm muscle or brain). In some embodiments, psilocybin is administered orally to the subject.

Methods of Treatment

It is to be understood by one of skill in the art that the methods of treatment comprising administering psilocybin, a prodrug of psilocybin, a metabolite of psilocybin, and/or a prodrug of a metabolite of psilocybin for the treatment of one or more indications as described herein also include: the use of psilocybin, a prodrug of psilocybin, a metabolite of psilocybin, and/ora prodrug of a metabolite of psilocybin in the manufacture of a medicament for the treatment of one or more indications as described herein; and the use of psilocybin, a prodrug of psilocybin, a metabolite of psilocybin, and/or a prodrug of a metabolite of psilocybin for the treatment of one or more indications as described herein.

In some embodiments, a method for treating a subject in need thereof comprises administering to the subject a therapeutically effective dose of psilocybin. In some embodiments, a method for treating a subject in need thereof comprises administering to the subject a therapeutically effective dose of psilocybin in a controlled environment, wherein the subject is provided with psychological support.

In some embodiments, a method for treating a subject in need thereof comprises at least one of the following:

(i) administering to the subject a therapeutically effective dose of psilocybin in a controlled environment, wherein the subject is provided with psychological support;

(ii) having the subject participate in one or more pre-administration psychological support session(s); and/or

(ii) having the subject participate in one or more post-administration psychological support session(s).

After administration of the psilocybin, the subject may not feel the effects of the drug for about 30 minutes to about 90 minutes. In some embodiments, the subject may not feel the effects of the drug for about 60 minutes. This period after administration and before the onset of effects will be referred to herein as the initial stage of the psilocybin session. The time marked by the onset of the drug's effects will be referred to herein as the early stage of the psilocybin session.

In some embodiments, the subject will experience the peak of the psilocybin's effects at about 1.5 hours to about 3.5 hours after administration thereof. The time period marked by the peak psilocybin experience will be referred to herein as the peak stage of the psilocybin session.

In some embodiments, the effects of the psilocybin may substantially wear off from about 4 hours to about 6 hours after administration. This time period will be referred to as the late stage of the psilocybin session.

In some embodiments, the subject's ability to reach a non-dual state (e.g., a mystical experience), or a sense of unity, boundlessness, ego-dissolution or transcendence correlates with positive clinical outcome. Each of these terms may be commonly defined as the breakdown of the usual relationship between self and other, whereby the subject might feel a oneness and increased sense of connectedness to the surrounding environment and/or the world at large.

In some embodiments, low levels of emotional arousal - which could indicate avoidance, lack of involvement or intellectualization - might, in some embodiments, be correlated with little or no improvement in treatment outcomes.

Factors that may influence the subjective experience of psilocybin include, for example, (i) dose, (ii) the mindset of the participant prior to the session, (iii) the setting of the session, (iv) the subject's ability to focus and stay with the experience, and/or (v) the subject's prior experience with psychedelics. These, and other factors, will be described in more detail below, along with ways to maximize therapeutic benefit of the psilocybin session.

Pre-Administration Psychological Support Sessions

In some embodiments, the subject participates in at least one psychological support session before administration of the psilocybin ("pre-administration psychological support session"). In some embodiments, a pre-administration psychological support session may be held about 1 month prior to the psilocybin administration. In some embodiments, a pre-administration psychological support session may be held about 2 weeks prior to the psilocybin administration. In some embodiments, a pre-administration psychological support session may be held about 1 week prior to the psilocybin administration. In some embodiments, a pre-administration psychological support session may be held about 3 days prior to the psilocybin administration. In some embodiments, a pre-administration psychological support session may be held about 1 day prior to the psilocybin administration. In some embodiments, a pre-administration psychological support session may be held on the same day as and prior to psilocybin administration.

In some embodiments, the subject may participate in one, two, three, four, five, six, seven, or eight pre-administration psychological support sessions. In some embodiments, the subject may participate in at least two pre-administration psychological support sessions. In some embodiments, the subject may participate in at least three pre-administration psychological support sessions. In some embodiments, the subject may participate in pre-administration psychological support sessions at least once per week, for at least two or three weeks prior to the psilocybin session. In some embodiments, the subject may additionally participate in a pre-administration psychological support session the day before the psilocybin session.

The pre-administration psychological support sessions may be individual sessions, wherein a subject meets one-on-one with a therapist. In some embodiments, the psychological support sessions may be group sessions, wherein more than one subject meets with a single therapist, or more than one therapist. In some embodiments, one or more of the subject's family members or friends may be present at the pre-administration psychological support session(s).

In some embodiments, the goals of the pre-administration session may include (i) establishing therapeutic alliance between subject and therapist; (ii) answering the subject's questions and addressing any concerns; and/or (iii) demonstrating and practicing the skills of self-directed inquiry and experiential processing. In some embodiments, the pre-administration psychological support sessions focus on discussion of possible psilocybin effects, and/or preparing subjects for the dosing session by practicing relevant therapeutic techniques to reduce avoidance and anxiety, eliciting relevant therapeutic goals, building rapport, and/or establishing therapeutic alliance. During the psychological support session, skills of self-directed inquiry and experiential processing may be demonstrated and/or practiced.

In some embodiments, breathing exercises meant to promote calm and/or ease anxiety may be demonstrated and/or practiced. In some embodiments, the breathing exercise comprise instructing the subject to focus on their breath and/or sensations associated with the breath throughout the body. For example the subject may be instructed to breathe in for a count of four, to hold their breath for a moment, and then to breathe out for a count of eight. In some embodiments, the therapist and subject may discuss the most helpful ways to support in case of emotional distress during the psilocybin session. In some embodiments, the subject is given access (e.g., online access) to materials concerning the safety and mechanism of action of psilocybin.

In some embodiments, the pre-administration psychological support sessions will serve to establish a therapeutic goal for the psilocybin session. In some embodiments, the subject suggests the therapeutic goal for herself or himself. In some embodiments, the therapist suggests the therapeutic goal to the subject. In some embodiments, the subject is reminded of the therapeutic goal during the pre-administration psychological support session.

In some embodiments, the therapists are trained to counsel the subject before, during, and/or after the psilocybin sessions. In some embodiments, the therapist will have mental health training. In some embodiments, the therapist will be a clinical psychologist, a psychiatrist, a social worker, a doctor or a nurse. In some embodiments, the therapist will meet the following criteria:

- Demonstrate independent clinical experience with direct subject care in areas that require counselling and psychotherapeutic skills;

- Current unrestricted professional license and/or good professional standing with no history of suspension, professional misconduct or disciplinary actions; and/or

- High level of openness to learning new approaches and receiving feedback.

Psychological Support During Psilocybin Sessions

During the treatment session, the subject may be supervised by one or more trained therapists. The therapist supervising the subject during the psilocybin session may be the same therapist from the subject's pre-administration psychological support session(s), or may be a different therapist. The therapist(s) may provide psychological support to the subject as necessary. As used herein, the term "psychological support" refers to any measure(s) taken by the therapist during the subject's psilocybin session to ensure the safety of the subject and maximize the clinical effectiveness of the psilocybin session. For example, the psychological support may be anything done by the therapist to (1) to ensure psychological safety of the subject; (2) to allow the subject's subjective experience to unfold naturally within the boundaries of the therapeutic intention set at the preparation; (3) to maintain participant's attention and awareness on the experience of the present moment thus allowing exposure and processing of the challenging emotional states and personal memories; and/or (4) to generate insights and solutions forthe resolution of challenging personal situations, conflicts and traumatic experiences. In some embodiments, support can be in the form of therapeutic touch, verbal reassurance, guided imagery and/or relaxation or breathing exercises. In some embodiments, the support may comprise reminders, encouragement, or active guiding. Typically, only one technique is applied at a time to allow for minimal intervention and interference with the subject's unique process.

In some embodiments, the main therapeutic goals of the therapist during the psilocybin session are to (i) minimize extreme anxiety, and (ii) provide appropriate support that enables the skills and processes of self-directed inquiry and experiential processing. In some embodiments, the therapist demonstrates genuine presence, patience, curiosity, and/or openness during the psilocybin session. "Presence" refers to being totally available and present with the subject during all stages of the psilocybin session, and exuding calmness at all times. "Curiosity" refers to interest and willingness to understand the subject's experience, without making assumptions. "Patience" means that the therapist facilitates the participant taking as much time as needed to explore their experiences without controlling the natural urge to help or direct the experience. "Openness" is the ability of the therapist to remain cognitively and experientially open, including a capacity to be

curious about how the subject's mind may uniquely choreograph the unfolding content of a session. This includes welcoming all emotions and expressions that might occur.

In some embodiments, the psychological support may comprise curious questioning. In this technique, brief, but detailed, questioning of subjects is used to help the subjects shift and sustain their attention towards different levels of cognition and emotions ("How does that make you feel?") Due to the applicability across a range of mental states and within various settings, the technique of curious questioning can typically be used safely and consistently during the psilocybin session, regardless of the quality or intensity of the experience of each subject.

In some embodiments, the level of psychological support will vary during the various stages of the subject's psilocybin experience (e.g., the initial stage, the early stage, the peak stage, and the late stage). In some embodiments, the type of psychological support will vary during the various stages of the subject's psilocybin experience *(e.g.,* the initial stage, the early stage, the peak stage, and the late stage). Because non-dual, ego-dissolution or "unitive" experiences have been shown to positively correlate with the magnitude and durability of the clinical response, the therapist will, in some embodiments, attend to such states with particular care.

In some embodiments, a subject may experience of a compromised sense of self during the subject's psilocybin experience. In some embodiments, this is interpreted from a psychoanalytic perspective as a disruption of ego-boundaries, which results in a blurring of the distinction between self-representation and object-representation, and precludes the synthesis of self-representations into a coherent whole. In some embodiments, non-dual, ego-dissolution or "unitive" experiences refer to an altered state of consciousness in which there is a reduction in the self-referential awareness that defines normal waking consciousness, resulting in a compromised sense of "self' and instead only a undivided background awareness, often characterised by a sense of unity or "oneness" that exceeds sensory or cognitive apprehension. In some embodiments, a non-dual experience is state of consciousness in which the subject-object dichotomy in normal waking consciousness is substituted for a unified background awareness that is centreless and undivided. In some embodiments, an ego dissolution experience is a spontaneously occurring state of consciousness where there is a reduction in the self-referential awareness that defines normal waking consciousness, resulting in a compromised sense of "self'. In some embodiments, a unitive experience is an experience characterised by a sense of unity or "oneness" that exceeds sensory or cognitive apprehension.

At the initial and early stage of the psilocybin session, psychological support may be used to reduce severe and/or prolonged anxiety. Anxiety prior to or during the onset of psilocybin effects

is not uncommon, and the therapists may be specially trained to recognize and actively manage subjects through such periods of anxiety until the subject is comfortable enough to continue on their own. In some embodiments, therapists validate the subject's feelings of anxiety without providing interpretations of perceptual disturbances or guiding subjects towards a particular image or memory, other than encouraging them to stay relaxed and open to the emergent experiences. For example, in some embodiments, the therapist may help alleviate anxiety using a grounding exercise. In such an exercise, the subject may be encouraged to pay attention to the sounds around them or to sensations on their skin when touching the bed/couch, ground, or other objects.

At the initial and early stage of the psilocybin session, the therapist may encourage the subject to lie down, practice relaxation and breathing exercises, and/or listen to calming music. In some embodiments, the therapist may remind the subject of the intention for the treatment session. For example, the therapist may ask the subject "What does feeling better or recovery feel like?" or any number of similar questions. Such reminders prior to the onset of or at the onset of psilocybin effects provide an implicit direction for the subjective experience during the psilocybin session. In some embodiments, the therapist may remind the subject that their primary task during this session is to simply collect new and interesting experiences which can then be discussed with the therapist after the session. The therapist may remind the participant of the purpose of the psilocybin therapy and the role of experiential processing, namely allowing the participant to be open and curious to whatever arises and encountering thoughts and feelings previously unknown to them. In some embodiments, the therapist emphasizes that this process inherently requires letting go and a willing passivity to the psychedelic experience.

During the acute onset of action, the subject might experience perceptual changes in visual, auditory or olfactory modes, and a range of unusual physical sensations. These experiences could be anxiety-provoking. In some embodiments, the therapist may practice reassuring "arm holding". This is where, upon the subject's request, a therapist will place his or her hand on the subject's wrist, arm, hand, or shoulder, as a way of helping the subject feel secure during this phase. This exercise may have been previously practiced during the pre-administration psychological support session.

In some embodiments, the therapist may encourage the subject to put on an eye mask, such as a Mindfold eyeshade. In some embodiments, the therapist encourages the subject to put on the eye mask before, during, or after the onset of the psilocybin's effects.

In some embodiments, the therapist may encourage the subject to put on headphones and listen to music. In some embodiments, the headphones reduce outside noise (e.g., "noise-cancelling" headphones). In some embodiments, the music is calming music such as instrumental

(e.g., classical) music. In some embodiments, the music comprises nature sounds and/or the sound of moving water *(e.g.,* ocean sounds). In some embodiments, the music comprises isochronic tones. In some embodiments, the music comprises moments of silence. In some embodiments, the music is emotionally evocative. In some embodiments, the music comprises a playlist which mirrors the pharmacodynamics of a typical high-dose psilocybin session: the initial stage, the early stage, the peak stage, and the late stage. In some embodiments, listening to music helps the subject to focus on their internal experience.

In case of prolonged anxiety or distress, therapists may, in some embodiments, actively guide participants through such experiences without interpreting or judging the experiences or giving advice. Once participants are comfortable, the therapist may encourage them to again engage in introspection.

During the peak and late stages of the psilocybin session, the therapist may encourage subjects to face and explore their experience, including the challenging ones. Therapists may direct subjects to participate self-directed inquiry and experiential processing to develop a different perspective on their personal challenges and conflicts, and to generate their own solutions. Such self-generated insights are not only therapeutic because of the emotional resolution, but also empowering to subjects.

As used herein, the term “self-directed inquiry” refers to directing attention to internal states. Subjects are encouraged to be curious about experiences in the present moment, including foreground and background thoughts, emotions, and physical sensations. During the preparation and integration stages, this inquiry might mean asking specific and detailed questions to help direct attention to internal states. However, during the period of drug action, inquiry might simply mean an attitude of openness to inner experiences.

As used herein, “experiential processing” refers to a participant’s ability to maintain full attention on the experiences that come into awareness through self-directed enquiry. This includes a willingness and ability to be with and/or move ‘in and through’ even uncomfortable or challenging thoughts, feelings, sensations or emotions, until discomfort is diminished or resolved.

In some embodiments, the therapist will employ a transdiagnostic therapy. In some embodiments, the transdiagnostic therapy is a Method of Levels (MOL) therapy. In still further embodiments, the MOL therapy comprises Self-Directed Enquiry and Experiential Processing. Typically, MOL uses brief, but detailed, curious questioning to help subjects shift and sustain their attention towards different levels of cognition and emotions (Carey, 2006; Carey, Mansell & Tai, 2015). The emphasis within MOL is on identifying and working with a subject’s underlying distress as opposed to just their symptoms. Such MOL related methods and techniques can include: (1)

Self-directed enquiry - directing attention to internal states. Participants are encouraged to be curious about experiences in the present moment, including foreground and background thoughts, emotions, and physical sensations; during the preparation and integration stages, such enquiry can mean asking specific and detailed questions to help direct attention to internal states, although for some embodiments, during the period of drug action, enquiry can refer to an attitude of openness to inner experiences; and (2) Experiential processing - sustained focus on the experience; refers to a participant's ability to maintain full attention on the experiences that come into awareness through self-directed enquiry. This includes a willingness and ability to be with and/or move 'in and through' even uncomfortable or challenging thoughts, feelings, sensations or emotions, until discomfort is diminished or resolved.

In some embodiments, the psychological support comprises mindfulness-based therapy or CBT cognitive behavioral therapy (CBT). In some embodiments, the psychological support is informed by a functional theory of human behavior called Perceptual Control Theory.

Occasionally, the subject will try to avoid emerging experiences or distract him/herself while trying to regain cognitive control over the unusual state of their mind. Such distractions may take different forms. For example, the subject might want to engage in a conversation or prematurely describe in detail their experience, visions or insights. When this occurs, the therapist may aim to remain as silent as possible, thereby enabling the subject and his/her inner experience to direct the course of the psilocybin session. In some embodiments, the therapist may use active listening skills paired with prompts to encourage the subject to continue focusing attention on present experiences, particularly if the participant engages the therapist in conversation. In another example, a subject might ask to go to the bathroom or have a drink of water. The sudden and urgent character of such requests might suggest that they are really trying to avoid emerging material. In such cases, the therapist may encourage the subject to stay with the experience by simply redirecting their attention. For example, the therapist may say something like, *"We will take a bathroom break at the end of this piece of music" or "I will get you water in a little while. Why don't you put the eye shades back on and relax for a few minutes?"* If the subject is trying to avoid a difficult experience, they might listen to the suggestion and relax.

In some embodiments, spontaneous movement such as shaking, stretching or dancing while engaging with the experience is accepted and often encouraged, unless the movement seems to be a way to distract oneself from the experience. In some embodiments, if the subject continues to move around a lot, reminders to periodically return to a lying down position and to actively focus inwards may be provided.

The therapist is not required to understand, support or even have an opinion about the nature or content of the subject's experiences, but the therapist may validate them and convey openness toward the subject's own view of them without dismissing or pathologizing any experience based on its unusual content. These experiences may provide the subject with a perspective that goes beyond identification with their personal narrative. In some embodiments, the therapist will validate one or more of the subject's experiences. In some embodiments, validation of the experiences simply means acknowledging the courage of opening up to the experience and the possibility that any experience will serve the intention of the session.

In some embodiments, a therapist provides psychological support for approximately 4-8 hours immediately after administration of the psilocybin. In some embodiments, the therapist uses guided imagery and/or breathing exercises to calm the subject and/or focus the subject's attention. In some embodiments, the therapist holds the hand, arm, or shoulder of the subject. In some embodiments, the therapist counsels the subject to do one or more of the following: (1) to accept feelings of anxiety, (2) to allow the experience to unfold naturally, (3) to avoid psychologically resisting the experience, (4) to relax, and/or (5) to explore the subject's own mental space.

In some embodiments, the therapist avoids initiating conversation with the subject, but responds if the subject initiates conversation. Typically, active intervention is kept to a minimum during the treatment experience. In some embodiments, the subject is encouraged to explore their own mental space, and simple guided imagery may be used to assist relaxation. "Guided imagery" refers to an exercise wherein the subject is asked to imagine a scene *(e.g.,* "Invite a scene, perhaps a landscape, and tell me where you find yourself'; "Imagine a place that feels safe to you.")

Post-Administration Psychological Support Session

In some embodiments, subjects may be encouraged to engage in post-administration integration sessions with their therapist. Integration is a process that involves processing, or embodying, a psychedelic experience within a therapeutic context. The process initially begins by the subject verbalising and reflecting upon any experience from the psilocybin session, and discussing it openly with their therapist. Successful integration of a psilocybin experience accommodates for emotional changes and comprises of translating experiences into new insights, perspectives, and subsequently new behaviors that can be used to benefit the subject's quality of life. New perspectives might in turn influence the participant's current knowledge or values and lead to new ways of relating to cognitions, emotions, behaviors and physical experiences.

In some embodiments, the goals and supportive methods used by the therapist throughout integration sessions should remain consistent, regardless of the intensity or content of the subjective experience explored by the subject. That said, the methods of support used by the therapist should accommodate for the full range of experiences a subject might have faced.

The integration process is not one that should be limited to the sessions with the therapist, and is a process that will likely continue to unfold beyond the visits in clinic. The therapist might encourage the participant to use methods such as spending time in nature, exercise, or creative expression to help facilitate the process further. The subject might also be encouraged to discuss experiences with their friends, family, and/or support network. The role of the integration sessions is not to cover and work on every experience, but to empower the participant by building their capacity to experientially process information safely. This enables the patient to continue self-directed integration, even outside of study visits.

In some embodiments, the subject participates in at least one psychological support session after administration of the psilocybin ("post-administration psychological support session"). In some embodiments, a post-administration psychological support session may be held on the same day as the psilocybin session, after the effects of the psilocybin have substantially worn off. In some embodiments, a post-administration psychological support session may be held the day after the psilocybin session. In some embodiments, a post-administration psychological support session may be held two days after the psilocybin session. In some embodiments, a post-administration psychological support session may be held three days after the psilocybin session. In some embodiments, a post-administration psychological support session may be held about one week after the psilocybin session. In some embodiments, a post-administration psychological support session may be held about two weeks after the psilocybin session. In some embodiments, a post-administration psychological support session may be held about one month after the psilocybin session. In some embodiments, a post-administration psychological support session may be held about three months after the psilocybin session. In some embodiments, a post-administration psychological support session may be held about six months after the psilocybin session. In some embodiments, a post-administration psychological support session may be held about twelve months after the psilocybin session.

In some embodiments, the subject may participate in one, two, three, four, five, six, seven, or eight post-administration psychological support sessions. In some embodiments, the subject may participate in at least two, or at least three post-administration psychological support sessions.

The post-administration psychological support sessions may be individual sessions, wherein a subject meets one-on-one with a therapist. In some embodiments, the psychological support sessions may be group sessions, wherein more than one subject meets with a single therapist, or more than one therapist. In some embodiments, one or more of the subject's family members or friends may be present at the post-administration psychological support session(s).

In some embodiments, the post-administration psychological support session may focus on integration of the psilocybin experience. Integration may involve processing a psychedelic experience in a therapeutic context. Integration may comprise psychological and somatic processing of the experience and a successful assimilation of insights into the subject's life for the purpose of growth, healing and/or well-being. During an integration session, a subject may be encouraged to talk about and reflect upon their experiences during the psilocybin session. In some embodiments, integration may comprise an external expression of the psilocybin experience, such as choice of words, tone of voice, gestures, and/or particular physical activities (yoga, exercise, bodywork, etc.) In some embodiments, integration comprises creatively expressing any insights or experiences gained during a psilocybin experience, for example through poetry, art, music/singing, dance, writing or drawing.

In some embodiments, the subject may be encouraged to reflect on both the thoughts and the feelings that he or she underwent during the psilocybin session, as well as to express those ideas and emotions into a concrete form that can serve as a tool for continuing to remember and integrate those lessons into the future. In some embodiments, the subject may be encouraged to acknowledge and connect with the range of the emotional cognitive and physical experiences of the psilocybin session, and relate them to current experiences in their life situation. This may be accomplished, for example, by discussing them initially with their therapist, and perhaps later with their family, friends, and support circle. Integration helps accommodate changes in emotional states as new insights are generated and integrated. When further explored through oscillating attention between foreground and background thoughts and emotions, such insights may lead to natural and effortless changes in perspectives or behaviors. In some embodiments, the integration process is not limited to initial integration meetings with the therapist, but continues to unfold spontaneously through a participant's own processing and actions in everyday life.

In the case of a low-intensity experience, the integration process might focus on the mental content that emerged during the hours of relaxation and introspection. This might also include reactions to what might have been an unremarkable experience, such as feeling of disappointment, anger, relief etc.

Psychological Support Provided Remotely

In some embodiments, psychological support may be provided remotely to a subject. For example, a therapist providing psychological support may not be in the same room, the same building, or in the same facility as a subject. Remote psychological support may be provided, for example by telephone *(i.e.,* by voice call), by video call or video conference, by text, or by email.

In some embodiments, a pre-administration therapy session is conducted remotely. In some embodiments, a post-administration therapy session *(e.g.,* an integration session) is conducted remotely.

In some embodiments, psychological support is provided remotely during the subject's psilocybin session. For example, in some embodiments, the subject takes the psilocybin in his or her own home, and a therapist provides psychological support by voice call, video call, text, email, etc., for at least 4-8 hours after the subject has taken the drug. In some embodiments, the subject takes the psilocybin in an administration facility as described herein, and the therapist provides psychological support to the subject a therapist provides psychological support by voice call, video call, text, email, etc., for at least 4-8 hours after the subject has taken the drug

In some embodiments, remote psychological support is provided to the subject using a digital or electronic system. In some embodiments, the digital or electronic system may comprise one or more of the following features:

- The digital or electronic system securely connects patients with one or more therapists or physicians for "virtual visits." These virtual visits may be introductory or routine.
- The digital or electronic system allows a subject to qualify, prequalify, or register for a psilocybin-based clinical trial, or a psilocybin-based psychological support session.
- The digital or electronic system is configured to help therapists and/or physicians manage and interact with patients. For example, the electronic system may allow the therapist to share documents with subjects, keep notes about sessions, or schedule future sessions.
- The digital or electronic system is configured to provide alerts for crisis intervention. For example, the digital or electronic system may allow the subject to contact the therapist if they are feeling anxiety or otherwise urgently need to talk to the therapist.

- The digital or electronic system is configured to help prepare the subject for a visit with their therapist and/or physician. For example, the digital or electronic system may contain information regarding psilocybin, the therapeutic protocol, etc.
- The digital or electronic system is configured to allow the therapist to provide psychological support during the subject's psilocybin session. For example, the system may comprise a video calling or chat feature.
- The digital or electronic system is configured to allow the therapist to provide psychological support during a post-administration session (e.g., an integration session).
- The digital or electronic system is configured to track the subject's adherence to the treatment regimen or goals.
- The digital or electronic system is configured to assess one or more clinical endpoints in the subject. For example the system may comprise one or more questionnaires or exercises for the subject to complete. Results may be made available to the subject's physician and/or therapist.

In some embodiments, the digital or electronic system is an "app" for use on a mobile phone or a computer. In some embodiments, the digital or electronic system is a website. In some embodiments, the digital or electronic system comprises a "chat" feature which allows communication between the subject and the therapist in real time. In some embodiments, the website comprises a video calling feature, which allows for the therapist to communicate with the subject using video communication. In some embodiments, the digital or electronic system is configured to allow a single therapist to provide psychological support to one or more subjects at or around the same time.

In some embodiments, psychological support sessions may be pre-recorded (e.g., audio or video recording) and provided to the subject for use at the subject's convenience via the digital or electronic system.

Administration Facility, "Set and Setting"

As used herein, the term "set and setting" refers to the subject's mindset ("set") and the physical and social environment ("setting") in which the user has the psilocybin session. In some embodiments, the psilocybin may be administered in a particular set and setting. In some embodiments, the set and setting is controlled, to the extent possible, to maximize therapeutic benefit of the psilocybin session.

In some embodiments, the psilocybin is administered by in a facility specifically designed for psilocybin administration. Administration of the psilocybin to the subject in a facility where the

subject feels safe and comfortable may help ease anxiety in the subject, and may facilitate maximum clinical benefit. Psilocybin may be administered to a subject, for example, in the subject's home or at a clinical facility.

In some embodiments, the psilocybin is administered to the subject in a facility (e.g., a room) with a substantially non-clinical appearance. For example, the psilocybin can be administered in a room that comprises soft furniture (e.g., plush couches, chairs, or pillows) and/or plants. In some embodiments, the room may be decorated using muted colors (e.g., greyed, dulled, or desaturated colors). In some embodiments, the light in the room is dimmed and/or light levels are kept or adjust to be relatively low. In some embodiments, the room lighting is adjusted for intensity and/or color. In some embodiments, a virtual reality or augmented reality system (e.g., computer with visual/graphical and auditory outputs) is used. In some embodiments, the room comprises a sound system, for example a high-resolution sound system. In some embodiments, the sound system can allow for simultaneous ambient and earphone listening. In some embodiments, the subject may bring meaningful photographs or objects into the administration room.

In some embodiments, the room comprises a couch. In some embodiments, the room comprises a bed. In some embodiments the room comprises more than one couch or bed, such as 2, 3, 4, 5, 6, 7, 8, 9, or 10 couches or beds. In some embodiments, the subject sits on or lies in the couch or bed for approximately 4-8 hours, or a substantial fraction thereof, immediately after administration of the psilocybin. In some embodiments, the subject listens to music for approximately 4-8 hours, or a substantial fraction thereof, immediately after administration of the psilocybin. In some embodiments, the subject wears an eye mask for approximately 4-8 hours, or a substantial fraction thereof, immediately after administration of the psilocybin. In some embodiments, the subject is provided with a weighted blanket.

In some embodiments, each subject is supervised by one therapist during the psilocybin session. In some embodiments, each subject is supervised by more than one therapist during the psilocybin session, such as two therapists, three therapists, four therapists, or five therapists. In some embodiments, one therapist multiple subjects, wherein each subject is participating in a psilocybin session. For example, one therapist may supervise two, three, four, five, six, seven, eight, nine, or ten subjects.

Embodiments of the disclosure include use of additional tools and/or technique(s) with dosage/administration, including various transcranial magnetic stimulation (TMS) methods and protocols, for example, prior or subsequent to one or more dosing(s), biofeedback devices, etc.

Some embodiments can be used with a digital health product or digital solution. Teachings of the disclosure include utilization of such digital health products and/or related digital biomarkers as diagnostic and/or prognostic tools for patient monitoring and management pre-treatment, during treatment, and/or post treatment. Digital biomarkers can include, by way of non-limiting example: Number of and / or time of phone calls/e-mails/texts; word length in text communication; Gestures used (taps, swipes, or other); Gyroscope derived information e.g. orientation of the phone; Acceleration of the phone; Keystroke patterns; Location derived information from GPS; facial expressions and/or microexpressions; voice or vocal markers; natural language processing; social media use; sleep patterns; specific words or emojis used or not used; and/or the like. For example, in one embodiment, a digital health product can be utilized to determine dosing amount and/or dosing frequency, indicator of a need for re-dosing, re-dosing amount, a warning or alert, as tracking of compliance, etc.

In some embodiments, methods of treatment can include providing a clearance time for a subject or patient, such one or more medications is not present or substantially cleared from the system of the subject/patient. For example, methods of treatment can be configured such that, upon administration, the subject is not taking other serotonergic medications such as: selective-serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and/or antipsychotics. In some embodiment, the method of treatment include treatment concurrently with one or more medications, including but not limited to selective-serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressants, and/or monoamine oxidase inhibitors. In some embodiments, the method include treatment such that subjects or patients take concomitant compounds or medications, including but not limited to benzodiazepines, cannabidiol (CBD) and/or other cannabinoids (e.g., THC (tetrahydrocannabinol); THCA (tetrahydrocannabinolic acid); CBD (cannabidiol); CBDA (cannabidiolic acid); CBN (cannabinol); CBG (cannabigerol); CBC (cannabichromene); CBL (cannabicyclol); CBV (cannabivarin); THCV (tetrahydrocannabivarin); CBDV (cannabidivarin); CBCV (cannabichromevarin); CBGV (cannabigerovarin); CBGM (cannabigerol monomethyl ether); CBE (cannabielsoin); CBT (cannabicitran); and/or the like) magnesium, Levomefolic acid, e.g., for a period of time prior to, just prior to, and/or at the same time as receiving psilocybin.

In some embodiments, the method includes treatment such that a subject has not taken one or more medications, particularly has not taken one or more serotonergic medications for at least 2 days, at least, 3 days, at least 4 days, at least 5 days, at least six days, at least 1 week, at least 2, 3, or 4 weeks before administration of the disclosed psilocybin compound.

In some embodiments, the method and/or treatment can comprise subperceptual-dosing (e.g., a dose of less than 3mg, 2.5mg, 2mg, 1.5mg, 1mg, 0.9mg, 0.8mg, 0.7mg, 0.6mg, 0.5mg, 0.4mg, 0.3mg, 0.2mg, or 0.1 mg) prior to and/or following the administration of a relatively larger single dose or multiple doses (given a few days to a few weeks apart), where the relatively larger single dose or multiple doses is one or more of 5mg or more, 10mg or more, 15mg or more, 20mg or more, 25mg or more, 30mg or more, 35mg or more, 40mg or more, 45mg or more, 50mg or more.

Embodiments of the disclosure include method utilizing a digital biomarker, for example, as a diagnostic and/or prognostic tool for patient management pre-, during and/ or post treatment with psilocybin wherein the digital biomarker is one or more biomarkers associated with executive function, cognitive control, working memory, processing speed, and/or emotional valence.

In some embodiments the digital biomarker is identified from patterns in smartphone use such as swipes, taps, and other touchscreen activities, andean be scientifically validated to provide measurements of subject status, such as cognition and mood, including, by way of non-limiting example, as disclosed in one or more of the following, each of which is herein expressly incorporated by reference for all purposes: US20170086727, US201 70258382, US20170258383, US201 70287348, US10148534, US9737759, and/or US10231651 .

Biomarkers which may serve as a diagnostic and / or prognostic tool for patient management pre, during and/ or post treatment may be identified using one or more of: Number of and / or time of phone calls/e-mails/texts; word length in text communication; Gestures used (taps, swipes, or other); Gyroscope derived information e.g. orientation of the phone; Acceleration of the phone; Keystroke patterns; Location derived information from GPS; facial expressions and/or microexpressions; voice or vocal markers; natural language processing; social media use; sleep patterns; specific words or emojis used or not used; and/or the like. In some embodiments, health components and/or connected biomonitors and/or smart devices/wearables can be utilized to collect information to be used in diagnostic and /or prognostic outputs. For example, in some embodiments, a heart rate monitor or similar device can collect a subject's data and heart rate variability (for example only, as disclosed in US1 0058253, the entirety of which is herein incorporated by reference) can be used to assess/determine a metric relating to the subject's current emotional state, relative change in emotional state, etc., which can be used in determining a new or follow-on treatment plan, adjusting a treatment plan, etc.

In accordance with a further aspect of the disclosure there is provided a method of assessing a subject pre, during and/ or post treatment of a central nervous system disorder to determine whether to provide a psilocybin treatment or a further psilocybin treatment comprising

monitoring one or more biomarkers associated with executive function, cognitive control, working memory, processing speed, and emotional valence, and determining the treatment based on an outcome. The method can further comprise the step of administering psilocybin for a first or a subsequent time.

In some embodiments, the biomarker is identified from patterns in smartphone use such as swipes, taps, and other touchscreen activities, and are scientifically validated to provide measurements of cognition and mood. For example, in some instances, the pattern is identified using one or more of: Number of and / or time of phone calls/e-mails/texts; word length in text communication; Gestures used (taps, swipes, or other); Gyroscope derived information e.g. orientation of the phone; Acceleration of the phone; Keystroke patterns; Location derived information from GPS; facial expressions and/or microexpressions; voice or vocal markers; natural language processing; social media use; sleep patterns; specific words or emojis used or not used; and/or the like.

Embodiments include a method of assessing a subject pre, during and/ or post treatment of a central nervous system disorder to determine whether to provide a psilocybin treatment or a further psilocybin treatment comprising monitoring one or more biomarkers associated with executive function, cognitive control, working memory, processing speed, and emotional valence, and determining the treatment based on an outcome; the method can further comprise administering psilocybin for a first or a subsequent time.

In some embodiments, the disclosure provides for treating 2 or more subjects, the method comprising administering to each subject a therapeutically-effective dose of psilocybin at the same time or substantially the same time (e.g., dosed within several minutes of each other, within 5, 10, 15, 20, 25, or 30 min of each other), wherein each subject is aware of the other subject also receiving treatment. In some embodiments, the subjects are in the same room. In some embodiments, the subjects are in different rooms.

In some embodiments, the disclosure provides a method of treating a subject, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, and providing a virtual reality / immersive reality digital tool. In some embodiments, the light in the room is dimmed and/or light levels are kept or adjusted to be relatively low. In some embodiments, darkened glasses or eye shades are provided. In some embodiments, the room lighting is adjusted for intensity and/or color. In some embodiments, a virtual reality or augmented reality system (e.g., computer with visual/graphical and auditory outputs) is used.

Subjects

In some embodiments, the subject is a male. In some embodiments, the subject is a female. In some embodiments, the female subject is pregnant or post-partum. In some embodiments, the subject is attempting to reduce or eliminate their use of a pharmaceutical agent, such as an anti-depressant or an anti-epileptic drug. In some embodiments, the subject is attempting to reduce or eliminate their use of the pharmaceutical agent before becoming pregnant, having surgery or other medical procedure, or starting to use different pharmaceutical agent.

The subject may be a geriatric subject, a pediatric subject, a teenage subject, a young adult subject, or a middle aged subject. In some embodiments, the subject is less than about 18 years of age. In some embodiments, the subject is at least about 18 years of age. In some embodiments, the subject is about 5-10, about 10-15, about 15-20, about 20-25, about 25-30, about 30-35, about 35-40, about 40-45, about 45-50, about 50-55, about 55-60, about 60-65, about 65-70, about 70-75, about 75-80, about 85-90, about 90-95, or about 95-1 00 years of age.

The subject may have a chronic disease or a terminal disease. In some embodiments, the subject may have a life-altering disease or condition (such as the loss of a limb or onset of blindness).

The subject may have recently been diagnosed with a disease, disorder, or condition. For example, the subject may have been diagnosed within 1 month, within 3 months, within 6 months, or within 1 year. In some embodiments, the subject may have been living with a disease, disorder, or condition for an extended period time, such as at least 6 months, at least 1 year, at least 3 years, at least 5 years, or at least 10 years.

In some embodiments, the subject may be a cancer patient, such as a Stage 4 or terminal cancer patient. In some embodiments, the subject may have been determined to have a limited time to live, such as less than 1 year, less than 6 months, or less than 3 months.

The subject may have previously taken a psychedelic drug, or may have never previously taken a psychedelic drug. For example, the subject may or may not have previously taken psilocybin, a psilocybin mushroom (“magic mushroom”), LSD (lysergic acid diethylamide or acid), mescaline, or DMT (N,N-Dimethyltryptamine).

In some embodiments, the subject may have previously taken one or more serotonergic antidepressants (e.g., selective serotonin reuptake inhibitors (SSRIs)). In some embodiments, the subject has never previously taken a serotonergic antidepressant. In some embodiments, the subject has not taken any serotonergic antidepressants for at least 2 weeks, at least 4 weeks, or at least 6 weeks prior to receiving psilocybin.

In some embodiments, the subject may have previously received electroconvulsive therapy (ECT). In some embodiments, the subject has not received any ECT for at least 2 weeks, at least 4 weeks, or at least 6 weeks prior to receiving psilocybin.

The subject may have a medical condition that prevents the subject from receiving a particular medical therapy (such as an SSRI or ECT). In some embodiments, the subject may have previously had an adverse reaction to a particular medical therapy (such as an SSRI or ECT). In some embodiments, a prior medical therapy (such as an SSRI or ECT) was not effective in treating a disease, disorder, or condition in the subject.

Diseases, Disorders, and/or Conditions to be Treated

Provided herein are methods of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin.

The methods described herein may be used to treat a variety of diseases, disorders, or conditions including particular psychiatric and neurological aspects of the diseases, disorders, or conditions.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin or a metabolite thereof, wherein the subject has at least one or more of the following diseases, disorders, or conditions: Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum Depression, Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder),

Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, or Kleptomania.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: a Neurocognitive Disorder due to Alzheimer's, Lewy Bodies, Traumatic Brain Injury, Prion Disease, Human Immunodeficiency Virus (HIV) Infection, Parkinson's, Huntington's; concussion; Chronic Traumatic Encephalopathy (CTE); Language Disorder, Speech Sound Disorder (Phonological Disorder); Childhood-Onset Fluency Disorder (Stuttering); Social (Pragmatic) Communication Disorder; Tourette's Disorder; Persistent (Chronic) Motor or Vocal Tic Disorder; Amnestic Disorder Due to Known Physiological Condition (possibly in ECT shock-resistant subjects); Transient Cerebral Ischemic Attack, Cerebral Infarction, Cerebral Bleeding, Progressive Supranuclear Ophthalmoplegia, or Retrograde Amnesia.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Autism, Autism Spectrum-Disorder, or Antisocial Personality Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Attention-Deficit/Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder or Unspecified Attention-Deficit/Hyperactivity Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Schizotypal (Personality) Disorder, Delusional Disorder, Schizophrenia, or Schizoaffective Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Insomnia Disorder, Hypersomnolence Disorder, Narcolepsy, or Primary Central Sleep Apnea.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Schizoid Personality Disorder, Schizotypal Personality Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, or Obsessive-Compulsive Personality Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Female Sexual Interest/Arousal Disorder, Male Hypoactive Sexual Desire Disorder, and Excessive Sexual Drive.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Bipolar I Disorder, Bipolar II Disorder, or Cyclothymic Disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Age-Related Hearing Loss or Tinnitus.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the has at least one of the following diseases, disorders, or conditions: Multiple Sclerosis, Cranial Nerve Disorder, Neuromyelitis Optica, Bell's Palsy, Guillain Barre Syndrome, Demyelinating Disease of Central Nervous System, or Chronic Inflammatory Demyelinating Polyneuritis.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject suffers from pain, such as phantom pain, chronic pain, or pain associated with another disease or disorder.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Myelopathy, Traumatic Brain Injury, Intellectual Disabilities, Mania, Neurodegeneration, Paraphilic disorders (e.g., Pedophilic Disorder), Suicidal Behavior Disorder, Nonsuicidal Self-Injury, Persistent Complex Bereavement Disorder, GI Tract Related Diseases (e.g., IBS),

Epilepsy, Sickle Cell Disease, locked-in syndrome, restless leg syndrome, stroke (such as ischemic stroke or hemorrhagic stroke), or Amyotrophic Lateral Sclerosis (ALS).

In some embodiments, the disclosure provides a method of treating a subject, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein after administration the subject exhibits an improvement in cognition. In some embodiments, the improvement in cognition is an improvement in attention, episodic memory, working memory, spatial memory, social cognition, executive function, and/or cognitive flexibility.

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Treatment Resistant Depression (TRD).

In some embodiments, the disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Major Depressive Disorder (MDD).

Pre-treatments and combination therapies

In some embodiments, the methods of treatment comprising administering psilocybin to a subject in need thereof further comprise pretreating the subject with magnesium before administration of the psilocybin. Sometimes, magnesium is administered daily for a least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, or at least 6 weeks before administration of the psilocybin. In some embodiments, about 10 mg to about 500 mg of magnesium are administered to the subject per day. In some embodiments, about 30 mg, about 75 mg, about 80 mg, about 130 mg, about 240 mg, about 310 mg, about 320 mg, about 360 mg, about 410 mg, about 400 mg, or about 420 mg are administered to the subject per day. In some embodiments the magnesium is administered to the subject on the same day as the psilocybin. In some embodiments, the magnesium is administered to the subject immediately before, concurrently with, or immediately after administration of the psilocybin. In some embodiments, magnesium supplements are administered to the subject until the subject's blood level for magnesium is about 1.5 to about 2.5 mEq/L. In some embodiments, psilocybin is not administered to the subject if the subject's blood level of magnesium is less than about 1.5 to about 2.5 mEq/L.

In some embodiments, the methods of treatment comprising administering psilocybin to a subject in need thereof further comprise pretreating the subject with niacin before administration of the psilocybin. Sometimes, niacin is administered daily for a least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, or at least 6 weeks before administration of the

psilocybin. In some embodiments, about 1 mg to about 5,000 mg of niacin are administered to the subject per day, for example about 1 mg to about 50 mg, about 10 mg to about 100 mg, about 100 mg to about 200 mg, about 1 mg to about 200 mg, about 100 mg to about 200 mg, about 10 mg to about 50 mg, about 10 to about 35 mg, about 100 mg to about 500 mg, or about 1,000 mg to about 3,000 mg. In some embodiments, about 10 mg, about 14 mg, about 15 mg, about 16 mg, about 20 mg, about 30 mg, about 35 mg, about 50 mg, about 60 mg, about 75 mg, about 100 mg, about 200mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1500 mg, about2000 mg, about 2500 mg, or about 3000 mg of niacin are administered to the subject per day (while avoiding any toxic exposure from excess niacin). In some embodiments, niacin is included as an ingredient / component, for example, to reduce risk of abuse and/or to improve efficacy. In some embodiments the niacin is administered to the subject on the same day as the psilocybin. In some embodiments, the niacin is administered to the subject immediately before, concurrently with, or immediately after administration of the psilocybin.

In some embodiments, psilocybin is administered to the subject in combination with one or more additional therapies. In some embodiments, psilocybin is administered to the subject in combination with one or more anti-depressant or anti-anxiety drugs, such as SSRIs, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or serotonin norepinephrine reuptake inhibitors (SNRIs).

In some embodiments, the disclosure provides a method of reducing anxiety in a subject undergoing treatment with psilocybin, the method comprising administering to the subject: i) psilocybin or a precursor or derivative thereof, and ii) one or more benzodiazepines.

In some embodiments, the one or more benzodiazepines are administered to the subject at or around the same time as the psilocybin or precursor or derivative thereof. In some embodiments, the one or more benzodiazepines are administered to the subject prior to administration of the psilocybin or precursor or derivative thereof, such as about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes before administration of the psilocybin or precursor or derivative thereof. In some embodiments, the one or more benzodiazepines are administered to the subject after the psilocybin or precursor or derivative thereof, such as about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90

minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes after administration of the psilocybin or precursor or derivative thereof.

In some embodiments, the one or more benzodiazepines are administered at a dose that is lower than doses typically used to treat anxiety, such as about 10%, 20%, 25%, 30%, 40%, 50%, or 75% of a typical dose. In some embodiments, the one or more benzodiazepines are administered at a dose that is approximately equivalent to doses typically used to treat anxiety. In some embodiments, the one or more benzodiazepines are administered at a dose that is higher than doses typically used to treat anxiety, such as about 125%, 150%, 175%, 200%, 250%, or 300% of a typical dose. In some embodiments, the one or more benzodiazepine is administered orally to the subject.

In some embodiments, the benzodiazepine is selected from the group consisting of adinazolam, alprazolam, bentazepam, bretazenil, bromazepam, bromazolam, brotizolam, camazepam, chlordiazepoxide, cinazepam, cinolazepam, clobazam, clonazepam, clonazolam, clorazepate, clotiazepam, cloxazolam, delorazepam, deschloroetizolam, diazepam, diclazepam, estazolam, ethyl carfluzepate, ethyl loflazepate, etizolam, flualprazolam, flubromazepam, flubromazolam, fluclotizolam, flunitrazepam, flunitrazolam, flurazepam, flutazolam, flutoprazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, meclonazepam, medazepam, metizolam, mexazolam, midazolam, nifoxipam, nimetazepam, nitemazepam, nitrazepam, nitrazolam, nordiazepam, norflurazepam, oxazepam, phenazepam, pinazepam, prazepam, premazepam, pyrazolam, quazepam, rilmazafone, temazepam, tetrazepam, and triazolam.

In certain embodiments, a patient is administered psilocybin or a precursor or derivative thereof as described herein along with one or more **5-HT$_{2A}$** specific antagonists and/or inverse agonists. In some embodiments, the patient is administered psilocybin or a precursor or derivative thereof and the one or more **5-HT$_{2A}$** specific antagonists and/or inverse agonists at the same time. In other embodiments, the patient is administered one or more 5-HT$_{2A}$ specific antagonists and/or inverse agonists prior to psilocybin administration, such as, but not limited to about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes before psilocybin administration. In some embodiments, the patient is administered one or more 5-HT$_{2A}$ specific antagonists and/or inverse agonists after psilocybin administration, such as, but not limited to about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90

minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes after psilocybin administration.

In certain embodiments, the one or more **5-HT$_{2A}$** specific antagonists and/or inverse agonists are administered at doses that are lower than doses typically used, e.g., about 10%, about 20%, about 25%, about 30%, about 40%, about 50%, or about 75% of a typical dose. In other embodiments, the one or more **5-HT$_{2A}$** specific antagonists and/or inverse agonists are administered at doses that are equivalent to doses typically used. In yet other embodiments, the one or more 5-HT$_{2A}$ specific antagonists and/or inverse agonists are administered at doses that are higher than doses typically used, e.g., about 125%, about 150%, about 175%, about 200%, about 250%, or about 300% of a typical dose.

Suitable 5-HT$_{2A}$ antagonists include but are not limited to, trazodone, mirtazapine, metergoline, ketanserin, ritanserin, nefazodone, clozapine, olanzapine, quetiapine, risperidone, asenapine, MDL-1 00907, cyproheptadine, pizotifen, LY-367,265, 2-alkyl-4-aryl-tetrahydro-pyrimido-azepine, 9-aminomethyl-9,10-dihydroanthracene (AMDA), haloperidol, chlorpromazine, hydroxyzine (atarax), 5-MeO-NBpBrT, niaprazine, altanserin, aripiprazole, etoperidone, setoperone, chlorprothixene, cinaserin, adatanserin, medifoxamine, rauwolscine, phenoxybenzamine, pruvanserin, deramciclane, nelotanserin, lubazodone, mepiprazole, xylamidine, R-(+)-alpha-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenethyl)]-4-piperidinemethanol (M100907), mianserin, AT 1015, DV 7028, eplivanserin, 4F 4PP, fanaserin, alpha-phenyl-1 -(2-phenylethyl)-4-piperidinemethanol (MDL 11,939), melperone, mesulergine, paliperidone, 1-[2-(3,4-Dihydro-1/-/-2-benzopyran-1-yl)ethyl]-4-(4-fluorophenyl)piperazine dihydrochloride (PNU 9641 5E), (2R,4R)-5-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-3-pyrrolidinol (R-96544), sarpogrelate, spiperone, ziprasidone, zotepine, and 7-[[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]carbonyl]-1/-/-indole-3-carbonitrile (EMD 281014).

Suitable 5-HT$_{2A}$ reverse agonists include but are not limited to, AC-90179, nelotanserin (APD-125), eplivanserin, pimavanserin (ACP-103), and volinaserin.

In certain embodiments, the 5-HT$_{2A}$ antagonist is selected from the compounds of Table I.

Table I: 5-HT2A antagonists

Acepromazine	Imipramine
Agomelatine	Lisuride
Amitriptyline	Loxapine
Amoxapine	Lurasidone
Amperozide	Mesoridazine
APD791	Methotrimeprazine

Aripiprazole	Methysergide
Aripiprazole lauroxil	Mianserin
Blonanserin	Mirtazapine
Brexpiprazole	Nefazodone
Butriptyline	Nortriptyline
Captodiame	Olanzapine
Cariprazine	Paliperidone
Chlorpromazine	Pimavanserin
Chlorprothixene	Pizotifen
Cinitapride	Promazine
Citalopram	Propiomazine
Clomipramine	PRX-08066
Clozapine	Quetiapine
Cyclobenzaprine	Risperidone
Cyproheptadine	Sertindole
Deramciclane	Thioproperazine
Desipramine	Thioridazine
Dosulepin	Tramadol
Doxepin	Trazodone
Epinastine	Trifluprom azine
Esmirtazapine	Trimipramine
Etoperidone	YKP-1358
Flibanserin	Yohimbine
Fluoxetine	Ziprasidone
Flupentixol	Zotepine
Fluspirilene	Zuclopenthixol
Iloperidone	

In some embodiments, the disclosure provides a method of reducing the negative side effects associated with a traumatic psychedelic experience in a patient undergoing treatment with psilocybin, the method comprising administering to the patient: i) psilocybin or a precursor or derivative thereof, and ii) one or more cannabinoids or cannabinoid derivatives.

In some embodiments, the cannabinoid is selected from the group consisting of THC (tetrahydrocannabinol), THCA (tetrahydrocannabinolic acid); CBD (cannabidiol); CBDA (cannabidiolic acid); CBN (cannabinol); CBG (cannabigerol); CBC (cannabichromene); CBL (cannabicyclol); CBV (cannabivarin); THCV (tetrahydrocannabivarin); CBDV (cannabidivarin); CBCV (cannabichromevarin); CBGV (cannabigerovarin); CBGM (cannabigerol monomethyl ether); CBE (cannabielsoin); and CBT (cannabicitran). In particular embodiments, the cannabinoid is CBD (cannabidiol).

In some embodiments, at least one symptom of a disease, disorder, or condition described herein is alleviated within 24 hours of administering psilocybin. In some embodiments, at least one symptom of the disease, disorder, orcondition is alleviated within 1 week of the administering. In some embodiments, at least one symptom of the disease, disorder, or condition is alleviated within 1 month of the administering. In some embodiments, at least one symptom of the disease, disorder, or condition is alleviated within 6 months of the administering. In some embodiments, at least one symptom of the disease, disorder, or condition is alleviated within 12 months of the administering.

In some embodiments, at least one symptom of the disease, disorder, or condition is alleviated for a period of at least 1 month after administering psilocybin. In some embodiments, at least one symptom of the disease, disorder, or condition is alleviated for a period of at least 3 months after the administering. In some embodiments, at least one symptom of the disease, disorder, or condition is alleviated for a period of at least 6 months after the administering. In some embodiments, at least one symptom of the disease, disorder, or condition is alleviated for a period of at least 12 months after the administering.

In some embodiments, no other treatment is administered to the subject to treat the disease, disorder, or condition before administration of the psilocybin. In some embodiments, no other treatment is administered to the subject to treat the disease, disorder, or condition after administration of the psilocybin.

Safety and Efficacy of Psilocybin

The present disclosure also relates to the safety and efficacy of the use of psilocybin as disclosed herein. The following is a non-exhaustive list of tests that can be used to determine the effects of psilocybin, and in particularthe psilocybin formulations as disclosed herein administered as disclosed herein.

In some embodiments, the Spatial Working Memory (SWM) test is utilized to evaluate the safety and efficacy of psilocybin as disclosed herein. SWM requires retention and manipulation of visuospatial information. Study subjects are required to find the blue tokens in the on-screen ‘boxes’. Boxes are searched by touching them to determine whether they contain a token. Once a token has been located it is ‘stacked’ in a column on the right of the screen. Study subjects then search for further tokens until they have all been located. The remaining tokens will thereafter only be found in boxes that have not so far yielded a token. Study subjects are explicitly told this is the case and it they revisit a box in which a token has been found they commit a ‘between error’, the usual primary metric for this test. Occasions on which the subject revisits a box in the same search are scored as a ‘within’ error. Many study subjects will adopt a search strategy via

which they systematically search the array of boxes. This is also scored by the Cambridge Neuropsychological Test Automated Battery system and yields a 'strategy' score. SWM performance is impaired by damage to the prefrontal cortex, especially the dorsolateral prefrontal cortex. Similarly, in neuroimaging studies in healthy volunteers, SWM performance is associated with activations in the dorsolateral and mid-ventrolateral prefrontal cortex. This test takes approximately 4 min to complete.

In some embodiments, the efficacy of psilocybin is evaluated using the spatial working memory between errors (SWMBE) score. In some embodiments, after treating according to the methods of the disclosure, a subject's SWMBE score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the efficacy of psilocybin is evaluated using the spatial working memory strategy (SWMS) score. In some embodiments, after treating according to the methods of the disclosure, a subject's SWMS score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the Rapid Visual Information Processing (RVP) test is utilized to evaluate the safety and efficacy of psilocybin. The RVP is a measure of sustained attention outputting measures of response accuracy, target sensitivity and reaction times. In this test, the study subject is required to monitor a stream of digits from 2 to 9 for specific sequences (e.g., 3-5-7) and to acknowledge detection of the sequence by touching the on-screen response button as quickly as possible after presentation of the third digit. Digits are presented pseudorandomly to create the possibility of 'false alarm' responses in which the first 2 digits of a sequence are not followed by a true target, e.g., when 3 is followed by a 5, but not then by a 7. In order to complete the task successfully study subjects must sustain attention to the white box in which the digits appear. Performance on this task is measured by the speed of response to the presentation of the final digit of a target, as well as the study subject's ability to detect specified sequences. This test takes approximately 7 min to complete. In some embodiments, performance on the Rapid Visual Information Processing test is reported using a RVP A Prime (RPVA) score. Higher scores on the RVPA indicated better performance. In some embodiments, after treating according to the

methods of the disclosure, a subject's RVPA score increases by between about 5 % and about 300 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment.

In some embodiments, the Paired Associates Learning (PAL) test is utilized to evaluate safety and/or efficacy of psilocybin. The PAL task is a measure of visuo-spatial memory in which study subjects are required to remember locations at which visual stimuli are located. Boxes are displayed on the screen and are "opened" in a randomized order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time and the subject must select the box in which the pattern was originally located. If the subject makes an error, the boxes are opened in sequence again to remind the subject of the locations of the patterns. Increased difficulty levels can be used to test high-functioning, healthy individuals. The primary metric for this test is the number of errors made. This test takes approximately 8 min to complete. Successful performance of the PAL test is dependent on functional integrity of the temporal lobe, particularly the entorhinal cortex. In some embodiments, the Paired Associates Learning total errors adjusted (PALTEA) score is used to assess the efficacy of psilocybin. In some embodiments, after treating according to the methods of the disclosure, a subject's PALTEA score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the efficacy and/or safety of psilocybin is evaluated using the cognitive flexibility panel test.

In some embodiments, the Emotion Recognition Task (ERT) test is utilized to evaluate the safety and/or efficacy of psilocybin. The ERT measures the ability to identify 6 basic emotions in facial expressions along a continuum of expression magnitude. In some embodiments, the ERT is performed according to the following protocol: Subjects are shown computer morphed images derived from the facial features of real individuals each showing a specific emotion, on a screen, one at a time. Each face is displayed for 200 ms and then immediately covered up, and the subject must select which emotion the face displayed from the six options (happy, sad, anger, fear,

surprise, disgust). The ERT percent correct (ERTPC) of correct responses (emotion selection) the subject made is assessed. A higher score indicates better performance. In some embodiments, after treating according to the methods of the disclosure, a subject's ERTPC increases by between about 5 % and about 300 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment.

In some embodiments, the Intra-Extra Dimensional Set Shift (IED) test is used to evaluate the safety and/or efficacy of psilocybin. The IED consists of four 7-item subscales, each of which taps a separate aspect of the global concept "empathy." In some embodiments, the Intra-Extra Dimensional Set Shift total errors (IEDYERT) score is used to assess the efficacy of psilocybin. In some embodiments, after treating according to the methods of the disclosure, a subject's IEDYERT score decreases by about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the One Touch Stockings (OTS) of Cambridge test is used to evaluate the safety and/or efficacy of psilocybin. The OTS is a test of executive function, based upon the Tower of Hanoi test. It assesses both the spatial planning and the working memory subdomains. This test takes approximately 10 min to perform. The OTS test reports an one touch stockings of Cambridge problems solved on first choice (OTSPSFC) score. A higher OTSPSFC score is associated with better executive function. In some embodiments, after treatment according to the methods of the disclosure, a subject's OTSPSFC score increases by between about 5 % and about 300 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, as compared to prior to treatment.

In some embodiments, verbal fluency is used to evaluate the safety and/or efficacy of psilocybin. In the verbal fluency test, the study subject is asked to name as many different category exemplars (e.g., 'animals') as they can in 1 min, subject to certain scoring rules, such as repetition. Successful performance on this test is reliant on the integrity of a number of cognitive abilities and especially those traditionally viewed as executive functions, such as planning and working memory. The primary metric for this test is the total number of acceptable words generated. In some embodiments, after treatment with psilocybin, a subject's verbal fluency category score improves by about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, as compared to prior to treatment.

In some embodiments, the Digit Span Forward (DSF) test is used to evaluate the safety and/or efficacy of psilocybin. DSF is used to measure number storage capacity. Subjects hear a sequence of digits and are tasked to recall the sequence correctly, with increasingly longer sequences being tested in each trial. The subject's span is the longest number of sequential digits that can accurately be remembered. Digit span tasks can be given forwards or backwards, meaning that once the sequence is presented, the subject is asked to either recall the sequence in normal or reverse order. For this study, subjects will be asked to recall the sequence in the order presented, i.e., Digit Span Forward. The primary metric for this test is the number of digit sequences successfully recalled. In some embodiments, after treatment with psilocybin, a subject's Digit Span Forward score improves by about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, as compared to prior to treatment.

In some embodiments, the Five Dimension Altered States of Consciousness questionnaire (5D-ASC) is utilized to evaluate the safety and/or efficacy of psilocybin. The 5D-ASC measures the acute drug effects using 5 primary dimensions and 11 lower-order scales to assess alterations in mood, perception and experience of self in relation to environment and thought disorder. The

5 dimensions include oceanic boundlessness, anxious ego dissolution, visionary restructuralization, auditory alterations and reduction of vigilance. In some embodiments, after treatment according to the methods of the disclosure, a subject experiences an increase on a dimension or a subscale compared to prior to treatment. The lower-order scales include "experience of unity," "spiritual experience," "blissful state," "insightfulness," "disembodiment," "impaired control of cognition," "anxiety," "complex imagery," "elementary imagery," "audio-visual synesthesia," and "changed meaning of percepts." In some embodiments, the increase is about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment.

In some embodiments, the Positive and Negative Affect Schedule (PANAS) is used to evaluate the safety and/or efficacy of psilocybin. The PANAS measures the acute emotional drug effects and comprises 2 mood scales that measure positive and negative affect. Positive affect refers to the propensity to experience positive emotions and interact with others positively. Negative affect involves experiencing the world in a more negative way. Subjects respond to 10 questions associated with negative affect and 10 questions associated with positive affect. The questions are scaled 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 effect while a lower score on the negative affect questions indicates less of a negative affect. In some embodiments, after treating according to the methods of the disclosure, a subject experiences a decrease in negative affect score of the PANAS, between about 5 % and about 100 %, for example about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, compared to prior to treatment. In some embodiments, after treating according to the methods of the disclosure, a subject experiences an increase in positive affect score of the PANAS, between about 5 % and about 100 %, for example about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %,

about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment.

In some embodiments, the NEO-Five Factor Inventory (NEO-FFI) test is used to evaluate the safety and/or efficacy of psilocybin. The NEO-FFI evaluates 5 broad domains of personality - Neuroticism, Extroversion, Openness, Agreeableness and Conscientiousness.

In some embodiments, the Symptom Checklist-90 item (SCL-90) questionnaire is used to evaluate the safety and/or efficacy of psilocybin. The SCL-90 is a relatively brief self-report psychometric instrument designed to evaluate a broad range of psychological problems and symptoms of psychopathology. In some embodiments, the SCL-90 is used to assess somatization, obsessive-compulsive behaviors, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism of a subject treated according to the methods of the disclosure. The 90 items in the questionnaire are scored on a 5-point Likert scale, indicating the rate of occurrence of the symptom during the time reference. In some embodiments, after treating according to the methods of the disclosure, a subject's SCL-90 score decreases by about 5 % to about 100 %, for example, by about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %.

In some embodiments, the Life Changes Inventory (LCI) questionnaire is utilized to evaluate the safety and/or efficacy of psilocybin. The LCI is designed as a questionnaire to investigate those variables present in the day-to-day experience of adults that might relate either to stability or decline of intellectual ability.

In some embodiments, Social Cognition Panel scales are utilized to evaluate the safety and/or efficacy of psilocybin. The social cognition panel scales comprise the pictorial empathy test (PET), reading the mind in the eyes test (RMET), social value orientation (SVO) test, the Toronto Empathy Questionnaire (TEQ), and the scale of social responsibility (SSR).

In some embodiments, the Pictorial Empathy Test (PET) is utilized to evaluate the effect of psilocybin on affective empathy.

In some embodiments, Reading the Mind in the Eyes Test (RMET) is utilized to evaluate the safety and/or efficacy of psilocybin. The RMET has 36 items, in which subjects are presented with a photograph of the eyes region of the face and must choose 1 of 4 adjectives or phrases to describe the mental state of the person pictured. A definition handout is provided at the beginning of the task and a practice item precedes the first trial.

In some embodiments, the Social Value Orientation (SVO) test is utilized to evaluate the safety and/or efficacy of psilocybin. The SVO Slider Measure has 6 primary items with 9 secondary (and optional) items. All of the items have the same general form. Each item is a resource allocation choice over a well-defined continuum of joint payoffs.

In some embodiments, after treating according to the methods of the disclosure, one or more of the subject's Social Cognition Panel Scales Score, i.e., PET, RMET, SVO, TEQ, and/or SSR score), improves by about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment.

In some embodiments, the Toronto Empathy Questionnaire (TEQ) is utilized to evaluate the safety and/or efficacy of psilocybin. The TEQ represents empathy as a primarily emotional process. The TEQ has exhibited good internal consistency and high test-retest reliability. The TEQ is a brief, reliable and valid instrument for the assessment of empathy. In some embodiments, after treating according to the methods of the disclosure, a subject's TEQ score increases by about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment.

In some embodiments, the Scale of Social Responsibility (SSR) is utilized to evaluate the safety and/or efficacy of psilocybin. The SSR measures perceptions regarding the importance of ethics and social responsibility.

In some embodiments, the Sheehan Suicidality Tracking Scale (SSTS) is utilized to evaluate the safety and/or efficacy of psilocybin. The SSTS is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0-4) ranging from "not at all" (0) to "extremely". The SSTS assesses the frequency of key phenomena and the overall time spent in suicidality.

In some embodiments, the Mini International Neuropsychiatric Interview (MINI) (version 7.0.2) is utilized to evaluate the safety and efficacy of psilocybin. The MINI is a brief structured interview for the major Axis I psychiatric disorders in DSM-5 and International Classification of Diseases-10. In some embodiments, the MINI is used to diagnose a subject with a disorder.

In some embodiments, the McLean Screening Instrument for Borderline Personality Disorder (MSIBPD) is utilized for evaluating the safety and/or efficacy of psilocybin. The MSIBPD is a useful screening tool for identifying the presence of DMS-IV borderline personality disorder.

In some embodiments, the Tellegen Absorption Scale is utilized for evaluating the safety and/or efficacy of psilocybin. The Tellegen Absorption Scale is a 34-item multidimensional measure that assesses imaginative involvement and the tendency to become mentally absorbed in everyday activities.

In some embodiments, the safety and/or efficacy of psilocybin is evaluated by physical examination. A physical examination, includes, but is not limited to, an examination of the subject's general appearance, including an examination of the skin, neck, eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities and musculoskeletal system.

In some embodiments, body weight and height of a subject are assessed. In some embodiments, body mass index is used to assess the safety and/or efficacy of psilocybin.

In some embodiments, an electrocardiogram (ECG) is utilized to evaluate the safety and/or efficacy of psilocybin. In some embodiments, a Standard 12-lead ECG is obtained.

In some embodiments, vital signs of a subject are used to evaluate safety and/or efficacy of psilocybin. Vital signs include, but are not limited to, blood pressure (BP), respiratory rate, oral body temperature and pulse. In some embodiments, blood pressure is taken after a subject has been sitting down for at least three minutes.

In some embodiments, clinical laboratory tests are utilized to evaluate the safety and/or efficacy of psilocybin. In some embodiments, the clinical laboratory tests include blood samples and/or urine samples. In some embodiments, hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count (with differential) and platelet count are measured to evaluate safety and/or efficacy of psilocybin. In some embodiments, albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (direct, indirect and total), calcium, chloride, creatine kinase, creatinine, y-glutamyl transferase, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, protein-total, sodium, blood urea nitrogen and/or uric acid are measured to evaluate the safety and/or efficacy of psilocybin.

In some embodiments, urine is tested for pregnancy and/or illicit drugs.

In some embodiments, the safety and/or efficacy of psilocybin are evaluated by measuring adverse events. Adverse events are classified as mild, moderate, or severe. A mild adverse event does not interfere in a significant mannerwith the subject's normal level of functioning. A moderate adverse event produces some impairment of functioning, but is not hazardous to the subject's health. A serious adverse event produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. Adverse events may include, for example, euphoric mood, dissociative disorder, hallucination, psychotic disorder, cognitive disorder, disturbances in attention, mood alterations, psychomotor skill impairments, inappropriate affects, overdoses, and intentional product misuse. In some embodiments, serious adverse events include death, life-threatening adverse events, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, and congenital anomaly/birth defect in the offspring of a subject who received psilocybin. In some embodiments, serious adverse events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Depression Assessments

In some embodiments, the sign or symptom of depression is measured in a subject before, during, or after treatment with the methods described herein. In some embodiments, the sign or symptom of depression is measured according to a diary assessment, an assessment by clinician or caregiver, a clinical rating scale, an imaging test, or a blood of CSF test.

In some embodiments, the sign or symptom of depression in a subject is measured using a neuropsychological assessment or clinical rating scale. In some embodiments, the neuropsychological assessment or clinical rating scale is the Hamilton Depression Rating Scale, the Clinical Global Impression (CGI) Scale, the Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), the Zung Self-Rating Depression Scale, the Raskin Depression Rating Scale, the Inventory of Depressive Symptomatology (IDS), the Quick Inventory of Depressive Symptomatology (QIDS), the Columbia-Suicide Severity Rating Scale, or the Suicidal Ideation Attributes Scale.

In some embodiments, the sign or symptom of depression in a subject is measured using the Hamilton Depression Rating (HAM-D) scale. The HAM-D scale is a 17-item scale that measures depression severity before, during, or after treatment. The scoring is based on 17 items and generally takes 15-20 minutes to complete the interview and score the results. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine items are scored

on a 3-point scale, ranging from 0 = not present to 2 = severe. A score of 10-13 indicates mild depression, a score of 14-17 indicates mild to moderate depression, and a score over 17 indicates moderate to severe depression. In some embodiments, after treatment with the methods described herein, the subject's HAM-D score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Clinical Global Impression (CGI) scale. The CGI scale is a 3-item scale that measures illness severity, global improvement or change, and therapeutic response. The CGI is rated on a 7-point scale, with the severity of illness measured using a range of responses from 1 (normal) through 7 (amongst the most severely ill subjects). In some embodiments, after treatment with the methods described herein, the subject's CGI score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Montgomery-Asberg Depression Rating Scale (MADRS). The MADRS scale is a 10-item scale that measures the core symptoms of depression. Nine of the items are based upon patient report, and 1 item is on the rater's observation during the rating interview. A score of 7 to 19 indicates mild depression, 20 to 34 indicates moderate depression, and over 34 indicates severe depression. MADRS items are rated on a 0-6 continuum with 0 = no abnormality and 6 = severe abnormality. In some embodiments, after treatment with the methods described herein, the subject's MADRS score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Beck Depression Inventory (BDI). The BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression. The items are rated on 0-3 continuum with 0 = no abnormality and 3 = severe abnormality. A score of 17-20 indicates

borderline clinical depression, a score of 21-30 indicates moderate depression, a score of 31-40 indicates severe depression, and over 40 indicates extreme depression. In some embodiments, after treatment with the methods described herein, the subject's BDI score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Zung Self-Rating Depression Scale. The Zung Self-Rating Depression Scale is a 20-item self-report questionnaire that measures the psychological and somatic symptoms associated with depression. The questionnaire takes about 10 minutes to complete, and items are framed in terms of positive and negative statements. Each item is scored on a Likert scale ranging from 1 to 4. A total score is derived by summing the individual item scores, and ranges from 20 to 80. Most people with depression score between 50 and 69, while a score of 70 and above indicates severe depression. In some embodiments, after treatment with the methods described herein, the subject's Zung Self-Rating Depression score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Raskin Depression Rating Scale. The Raskin Depression Rating Scale measures baseline levels of depression and change in depression severity overtime. Each item is scored on a scale ranging from 1 to 5 with 1 = not at all and 5 = very much. A total score is derived by summing the individual item scores, and scores of 9 or greater represents moderate depression. In some embodiments, after treatment with the methods described herein, the subject's Raskin Depression Rating Scale score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Inventory of Depressive Symptomatology (IDS). The IDS is a 30-item inventory that measures depressive signs and symptoms. Each item is scored on a scale of 0 to 3 with 0 = absence of

pathology and 3 = severe pathology. A total score is derived by summing the individual item scores; scores between 26-38 indicates mild depression, scores between 39-48 indicate moderate depression, and scores 49 or greater indicate severe depression. In some embodiments, after treatment with the methods described herein, the subject's IDS score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Quick Inventory of Depressive Symptomatology (QIDS). The QIDS is a 16-item inventory that measures depressive signs and symptoms. Each item is scored on a scale of 0 to 3 with 0 = absence of pathology and 3 = severe pathology. A total score is derived by summing the individual item scores; scores between 11-15 indicate moderate depression, scores between 16-20 indicate severe depression, and scores 21 or greater indicate very severe depression. In some embodiments, after treatment with the methods described herein, the subject's QIDS score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Young Mania Rating Scale (YMRS). The YMRS is an 11-item inventory that measures manic signs and symptoms. There are 4 items that are graded on a 0 to 8 scale, ranging from 0 = absent to 8 = severe. The remaining 7 items are graded on a 0 to 4 scale, ranging from 0 = absent to 4 = severe. A total score is derived by summing the individual item scores; scores between 9-15 indicate mild mania, scores between 16-25 indicate moderate mania, and scores 26 or greater indicate severe mania. In some embodiments, after treatment with the methods described herein, the subject's YMRS score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS measures the severity of suicidal ideation and behavior. The scale contains 10 binary questions (no = 0 points and yes =

1 point) and each question addresses a different component of the subject's suicidal ideation severity and behavior. A subject is considered to have suicidal ideation and/or behavior if they answer "yes" to any of the 10 questions. In some embodiments, after treatment with the methods described herein, the subject's C-SSRS score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using the Suicidal Ideation Attributes Scale (SIDAS). The SIDAS measures the presence and severity of suicidal thoughts. The scale contains 5 questions measured on a 10-point scale with 0 = never and 10 = always. Total scores are calculated as the sum of the 5 items and range from 0 to 50. Scores of 21 or greater indicate high risk of suicidal behavior. In some embodiments, after treatment with the methods described herein, the subject's SIDAS score decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom in subjects with depression is measured using a Spielberger's Trait and Anxiety Inventory, a Generalized Anxiety Disorder 7-Item Scale, a Warwick-Edinburgh Mental Wellbeing Scale, a Flourishing Scale, a Snaith Hamilton Anhedonia Pleasure Scale, a Life Orientation Test, a Meaning in Life Questionnaire, a Brief Resilience Scale, a Dysfunctional Attitudes Scale, a 44-item Big Five Inventory, a Peters 21-item Delusional Inventory, an Examination of Anomalous Self- Experience, a Ruminative Responses Scale, a White Bear Suppression Inventory, a Barrett Impulsivity Scale, a Brief Experiential Avoidance Questionnaire, a Modified Tellegen Absoprtion Questionnaire, a Scale to Assess Therapeutic Relationship, Credibility/Expectancy Questionnaire, a Connectedness to Nature Scale, a Political Perspective Questionnaire, a Social Connectedness Scale, a Bech-Rafaelsen Mania Rating Scale, a Revised Santa Clara brief compassion scale, a Gratitude Questionnaire, a Short Suggestibility Scale, a Rosenberg Self-Esteem Scale, a Universality Subscale of the Spiritual Transcendence Scale, an Oxford Questionnaire on the Emotional Side-effects of Antidepressants, a Lauks Emotional Intensity Scale, Sexual Dysfunction Questionnaire, a Brief Index of Sexual Functioning for Women, a Sexual Perceptions Questionnaire, a Barnes Akathisia Rating Scale, a Work Productivity and Activity Impairment Questionnaire, a Work and Social

Adjustment Scale, a Connectedness Questionnaire, a Standard Assessment of Personality, a Positive and Negative Syndrome Scale, a Mastery Insight Scale, a Self-Reflection and Insight Scale, a Psychological Insight Scale, a Metaphysical Beliefs Questionnaire, a Spiritual Bypassing Scale, an Adverse Childhood Experience Questionnaire, a Therapeutic Music Experience Questionnaire, a Setting Questionnaire, an Absorption in Music Scale, a Psychedelic Predictor Scale, a Surrender Scale, a EuroQOL-5 Dimension-3 Level Scale, or any combinations thereof. In some embodiments, after treatment with the methods described herein, the sign or symptom of depression measured using any of the assessments listed above decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression in a subject is measured using an imaging test before, during, or after treatment with the methods described herein. In some embodiments, the imaging test is a CT scan. In some embodiments, the imaging test is a functional MRI scan. In some embodiments, the functional MRI scan measures the blood oxygen level-dependent (BOLD) response as an indicator of brain activity and/or functional connectivity. In some embodiments, the BOLD response is measured in the subject at resting state, in response to emotional faces, or in response to music. In some embodiments, after treatment with the methods described herein, the BOLD response in a region of the brain increases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment. In some embodiments, after treatment with the methods described herein, the BOLD response in the amygdala increases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment. In other embodiments, after treatment with the methods described herein, the BOLD response in a region of the brain decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment. In some embodiments, after treatment with the

methods described herein, the BOLD response in the amygdala decreases by between about 5 % and about 100 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, or about 100 %, or more, compared to prior to treatment.

In some embodiments, the sign or symptom of depression is measured using a marker for depression in the blood or cerebral spinal fluid. In some embodiments, the marker for depression is measured in the subject before, during, or after treatment with the methods or compositions described herein. In some embodiments, the marker for depression is red blood cell folate, serum folate, vitamin B12, plasma homocysteine, serum methylfolate, and/or testing for one or more of brain-derived neurotrophic factor (BDNF) Val66Met, bone morphogenetic protein rs41271330, and/or 5-HTTLPR polymorphisms. In some embodiments, the marker for depression decreases by between about 5 % and about 300 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment. In other embodiments, the marker for depression increases by between about 5 % and about 300 %, for example, about 5 %, about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, about 50 %, about 55 %, about 60 %, about 65 %, about 70 %, about 75 %, about 80 %, about 85 %, about 90 %, about 95 %, about 100 %, about 110 %, about 120 %, about 130 %, about 140 %, about 150 %, about 160 %, about 170 %, about 180 %, about 190 %, about 200 %, about 210 %, about 220 %, about 230 %, about 240 %, about 250 %, about 260 %, about 270 %, about 280 %, about 290 %, or about 300 %, or more, compared to prior to treatment.

NUMBERED EMBODIMENTS OF THE DISCLOSURE

In addition to the disclosure above, the Examples below, and the appended claims, the disclosure sets forth the following numbered embodiments.

1. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment-Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, or Kleptomania.

2. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Neurocognitive Disorders due to Alzheimer's, Lewy Bodies, Traumatic Brain Injury, Prion Disease, HIV Infection, Parkinson's, or Huntington's; concussion; chronic traumatic encephalopathy (CTE); Language Disorder, Speech Sound Disorder (Phonological Disorder); Childhood-Onset Fluency Disorder (Stuttering); Social (Pragmatic) Communication Disorder; Tourette's Disorder; Persistent (Chronic) Motor or Vocal Tic Disorder; Amnestic Disorder Due to Known Physiological Condition; Transient Cerebral

Ischemic Attack, Cerebral Infarction, Cerebral Bleeding, Progressive Supranuclear Ophthalmoplegia, or Retrograde Amnesia.

3. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions:Autism Spectrum Disorder, or Antisocial Personality Disorder.

4. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the followings diseases, disorders, or conditions: Attention-Deficit/Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder; or Unspecified Attention-Deficit/Hyperactivity Disorder.

5. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Schizotypal (Personality) Disorder, Delusional Disorder, Schizophrenia, or Schizoaffective Disorder

6. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Female Sexual Interest/Arousal Disorder, Male Hypoactive Sexual Desire Disorder, or Excessive Sexual Drive.

7. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Bipolar I Disorder, Bipolar II Disorder, or Cyclothymic Disorder.

8. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Insomnia Disorder, Hypersomnolence Disorder, Narcolepsy, or Primary Central Sleep Apnea.

9. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Schizoid Personality Disorder, Schizotypal Personality Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, or Obsessive-Compulsive Personality Disorder.

10. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: age-related hearing loss or tinnitus.

11. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Multiple Sclerosis, Cranial Nerve Disorder, Neuromyelitis Optica, Bell's Palsy, Guillain Barre Syndrome, Demyelinating Disease of Central Nervous System, or Chronic Inflammatory Demyelinating Polyneuritis.

12. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject suffers from pain.

13. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Myelopathy, Traumatic Brain Injury, Intellectual Disabilities, Mania, Neurodegeneration, Paraphilic disorders (e.g. Pedophilic Disorder), Suicidal Behavior Disorder, Nonsuicidal Self-Injury, Persistent Complex Bereavement Disorder, Gastrointestinal Tract Related Diseases, Epilepsy, Sickle Cell Disease, locked-in syndrome, restless leg syndrome, stroke, or Amyotrophic Lateral Sclerosis (ALS).

14. A method of treating a subject, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein after administration the subject exhibits an improvement in cognition.

15. The method of embodiment 14 wherein the improvement in cognition is an improvement in attention, episodic memory, working memory, spatial memory, social cognition, executive function, and/or cognitive flexibility.

16. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Treatment Resistant Depression (TRD).

17. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Major Depressive Disorder (MDD).

18. The method of any one of embodiments 1-17 wherein the subject is a mammal.

19. The method of embodiment 18, wherein the subject is a human.

20. The method of any of embodiments 1-19, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in

the form of Polymorph A, wherein the crystalline psilocybin comprises at least 90% by weight of Polymorph A.

21. The method of embodiment 20, wherein the crystalline psilocybin comprises at least 95% by weight of Polymorph A.

22. The method of embodiment 20 or21 , wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

23. The method of any of embodiments 1-22, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

24. The method of embodiment 23, wherein the highly pure crystalline psilocybin comprises at least 90% by weight of Polymorph A.

25. The method of embodiment 24, wherein the highly pure crystalline psilocybin comprises at least 95% by weight of Polymorph A.

26. The method of any one of embodiments 20-25, wherein the highly pure crystalline psilocybin is further characterized having either:

(i) a water content of <0.5% w/w; or

(ii) <0.5% w/w loss in the TGA thermogram between 25° C and 200° C.

27. The method of any of embodiments 20-26, wherein the highly pure crystalline psilocybin is further characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 155°C and a second onset temperature of between 205 and 220°C.

28. The method of any one of embodiments 20-27, wherein the highly pure crystalline psilocybin is further characterized by one or more of the following: (a) a loss on drying of no more than 2% w/w; (b) residue on ignition of no more than 0.5% w/w; (c) assay (on a dry basis) of 95-103% by weight as measured by HPLC; (d) residual solvent content of no more than 3000 ppm methanol; 5000 ppm ethanol, 720 ppm THF, and 890 ppm toluene, as measured by HRGC; (e) phosphoric acid content of no more than 1% w/w as measured by ^{31}P NMR; and (f) Inductively Coupled Plasma Mass Spectrometry (ICP-MS) elemental analysis of: (i) no more than 1.5ppm Cd; (ii) no more than 1.5ppm Pb; (iii) no more than 4.5ppm As; (iv) no more than 9.0ppm Hg; (v) no more than 15ppm Co; (vi) no more than 30ppm V; (vii) no more than 60ppm Ni; (viii) no more than 165ppm Li; and (ix) no more than 30ppm Pd.

29. The method of any of embodiments 20-28, wherein the highly pure crystalline psilocybin has no single impurity of greater than 0.5%.

30. The method of any of embodiments 20-29, wherein the dosage form further comprises about 5 to 40 mg of the highly pure crystalline psilocybin.

31. The method of embodiment 30, wherein the dosage form comprises 5 mg of highly pure crystalline psilocybin.

32. The method of embodiment 30, wherein the dosage form comprises about 10 mg of highly pure crystalline psilocybin.

33. The method of embodiment 30, wherein the dosage form comprises about 35 mg of highly pure crystalline psilocybin.

34. The method of any of embodiments 20-33, wherein the dosage form comprises silicified microcrystalline cellulose.

35. The method of embodiment 34, wherein the silicified microcrystalline cellulose has a particle size range from about 45 to 150 microns.

36. The method of any of embodiments 20-35, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns and the second variant has a particle size of about 90 to 150 microns.

37. The method of embodiment 36, wherein about 30% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 70% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

38. The method of embodiment 36, wherein about 20% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 80% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

39. The method of embodiment 36, wherein about 15% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 85% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

40. The method of embodiment 36, wherein about 15% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 85% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

41. The method of embodiment 36, wherein the dosage form comprises 5 mg of crystalline psilocybin in the form of Polymorph A, 12.5 mg of SMCC 50, 79.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide and 1 mg sodium stearyl fumarate.

42. The method of embodiment 36, wherein the dosage form comprises 1 mg of crystalline psilocybin in the form of Polymorph A, 20.5 mg of SMCC 50, 75.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide, and 1 mg sodium stearyl fumarate.

43. The method any one of embodiments 20-42, wherein the dosage form is an oral dosage form.

44. The method of embodiment 43, wherein the dosage form is a capsule.

45. The method of embodiment 43, wherein the dosage form is a tablet.

46. The method of any one of embodiments 1-45, wherein at least one dose of psilocybin is administered to the subject.

47. The method of embodiment 46, wherein the at least one dose of psilocybin is in the range of about 0.1 mg to about 100 mg.

48. The method of embodiment 47, wherein the dose of psilocybin is about 1 mg.

49. The method of embodiment 47, wherein the dose of psilocybin is about 10 mg.

50. The method of embodiment 47, wherein the dose of psilocybin is about 25 mg.

51. The method of any one of embodiments 1-50, wherein more than one dose of psilocybin is administered to the subject.

52. The method of embodiment 51, wherein at least two doses of psilocybin are administered to the subject.

53. The method of any one of embodiments 51-52, wherein the psilocybin is administered once per day.

54. The method of any one of embodiments 51-52, wherein the psilocybin is administered at least once per week.

55. The method of any one of embodiments 51-52, wherein the psilocybin is administered at least twice per week.

56 The method of any one of embodiments 51-52, wherein the psilocybin is administered at least once per month.

57. The method of any one of embodiments 51-52, wherein the psilocybin is administered at least twice per month.

58. The method of any one of embodiments 51-52, wherein the psilocybin is administered at least once every three months.

59. The method of any one of embodiments 51-52, wherein the psilocybin is administered at least once every six months.

60. The method of any one of embodiments 51-52, wherein the psilocybin is administered at least once every 12 months.

61. The method of any one of embodiments 79-88, wherein each dose of psilocybin administered is in the range of about 0.1 mg to about 100 mg.

62. The method of embodiment 61, wherein each dose of psilocybin administered is about 1 mg.

63. The method of embodiment 61, wherein each dose of psilocybin administered is about 10 mg.

64. The method of embodiment 61, wherein each dose of psilocybin administered is about 25 mg.

65. The method of any one of embodiments 46-65, wherein the psilocybin is administered by one of the following routes: oral, parenteral, topical, inhalation, rectal, transmucosal, intranasal, buccal, vaginal, intrathecal, intraocular, transdermal, in utero, intralymphatic, or by direct tissue or organ injection.

66. The method of embodiment 65, wherein the psilocybin is administered orally.

67. The method of any one of embodiments 1-66, wherein the subject participates in at least one psychological support session before administration of the psilocybin.

68. The method of embodiment 67, wherein the subject participates in at least three psychological support sessions before administration of the psilocybin.

69. The method of any one of embodiments 67-68, wherein the at least one therapeutic intention is discussed during the psychological support session.

70. The method of any one of embodiments 67-69, wherein self-directed inquiry and experiential processing are practiced during the psychological support session.

71. The method of any one of embodiments 67-70, wherein the subject participates in at least one psychological support session after administration of the psilocybin.

72. The method of embodiment 71, wherein the subject participates in at least three psychological support sessions after administration of the psilocybin.

73. The method of any one of embodiments 67-72, wherein the psilocybin is administered to the subject in a room with a substantially non-clinical appearance.

74. The method of embodiment 73, wherein the room comprises soft furniture.

75. The method of any one of embodiments 73-74, wherein the room is decorated using muted colors.

76. The method of any one of embodiments 73-75, wherein the room comprises a high-resolution sound system.

77. The method of any one of embodiments 73-76, wherein the room comprises a bed or a couch.

78. The method of embodiment 77, wherein the subject lies in the bed or on the couch for approximately 4-8 hours, or a substantial fraction thereof, after administration of the psilocybin.

79. The method of any one of embodiments 73-78, wherein the subject listens to music for approximately 4-8 hours, ora substantial fraction thereof, after administration of the psilocybin.

80. The method of any one of embodiments 73-79, wherein the subject wears an eye mask for approximately 4-8 hours, or a substantial fraction thereof, after administration of the psilocybin.

81. The method of any one of embodiments 67-80, wherein a therapist provides psychological support to the subject for approximately 4-8 hours after administration of the psilocybin.

82. The method of embodiment 81, wherein the therapist uses guided imagery and/or breathing exercises to calm the subject and/or focus the subject's attention.

83. The method of embodiment 81, wherein the therapist provides reassuring physical contact with the subject.

84. The method of embodiment 83, wherein the therapist holds the hand, arm, or shoulder of the subject.

85. The method of embodiment 81, wherein the therapist encourages the subject to perform self-directed inquiry and experiential processing.

86. The method of embodiment 81, wherein the therapist reminds the subject of at least one therapeutic intention.

87. The method of embodiment 81, wherein the therapist counsels the subject to do one or more of the following: (1) to accept feelings of anxiety, (2) to allow the experience to unfold naturally, (3) to avoid psychologically resisting the experience, (4) to relax, and/or (5) to explore the subject's own mental space.

88. The method of embodiment 81, wherein the therapist does not initiate conversation with the subject.

89. The method of embodiment 81, wherein the therapist responds to the subject if the subject initiates conversation.

Numbered Embodiments for Depression

1. A method of treating depression in a subject in need thereof, the method comprising administering an effective amount of psilocybin or an active metabolite thereof to the subject.

2. The method of embodiment 1, wherein the subject has major depressive disorder, atypical depression, bipolar disorder, catatonic depression, a depressive disorder due to a

medical condition, postpartum depression, premenstrual dysphoric disorder, or seasonal affective disorder.

3. The method of embodiment 2, wherein the subject has major depressive disorder.

4. The method of embodiment 2, wherein the subject has bipolar disorder.

5. The method of embodiment 4, wherein the subject has bipolar disorder I.

6. The method of embodiment 4, wherein the subject has bipolar disorder II.

7. The method of any one of embodiments 1-6, wherein the depression is resistant to treatment.

8. The method of any one of embodiments 1-7, wherein at least one sign or symptom of depression is reduced.

9. The method of embodiment 8, wherein the sign or symptom of depression is depressed mood, diminished interest in activities, weight loss or gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate or indecisiveness, or suicidal ideation or behavior.

10. The method of embodiment 9, wherein the sign or symptom of depression is measured according to a diary assessment, an assessment by clinician or caregiver, a clinical rating scale, or by functional MRI.

11. The method of embodiment 10, wherein the clinical depression rating scale is a Quick Inventory of Depressive Symptomatology (QIDS)-16 scale, a QIDS-16 daily scale, a Hamilton Depression Rating scale, a Beck Depression Inventory scale, a Mongomery-Asberg Depression Rating Scale, a Clinical Global Impression Scale, a Zung Self-Rating Depression Scale, a Raskin Depression Rating Scale, and/or Young Mania Rating Scale.

12. The method of embodiment 10, wherein the sign or symptom of depression is measured using a Spielberger's Trait and Anxiety Inventory, a Generalized Anxiety Disorder 7-Item Scale, a Warwick-Edinburgh Mental Wellbeing Scale, a Flourishing Scale, a Snaith Hamilton Anhedonia Pleasure Scale, a Life Orientation Test, a Meaning in Life Questionnaire, a Brief Resilience Scale, a Dysfunctional Attitudes Scale, a 44-item Big Five Inventory, a Peters 21-item Delusional Inventory, an Examination of Anomalous Self- Experience, a Ruminative Responses Scale, a White Bear Suppression Inventory, a Barrett Impulsivity Scale, a Brief Experiential Avoidance Questionnaire, a Modified Tellegen Absorption Questionnaire, a Scale to Assess Therapeutic Relationship, Credibility/Expectancy Questionnaire, a Connectedness to Nature Scale, a Political Perspective Questionnaire, a Social Connectedness Scale, a Bech-Rafaelsen Mania Rating Scale, a Revised Santa Clara brief compassion scale, a Gratitude Questionnaire, a Short Suggestibility Scale, a Rosenberg Self-Esteem Scale, a Universality Subscale of the

Spiritual Transcendence Scale, an Oxford Questionnaire on the Emotional Side-effects of Antidepressants, a Lauks Emotional Intensity Scale, Sexual Dysfunction Questionnaire, a Brief Index of Sexual Functioning for Women, a Sexual Perceptions Questionnaire, a Barnes Akathisia Rating Scale, a Work Productivity and Activity Impairment Questionnaire, a Work and Social Adjustment Scale, a Connectedness Questionnaire, a Standard Assessment of Personality, a Positive and Negative Syndrome Scale, a Mastery Insight Scale, a Self-Reflection and Insight Scale, a Psychological Insight Scale, a Metaphysical Beliefs Questionnaire, a Spiritual Bypassing Scale, an Adverse Childhood Experience Questionnaire, a Therapeutic Music Experience Questionnaire, a Setting Questionnaire, an Absorption in Music Scale, a Psychedelic Predictor Scale, a Surrender Scale, a EuroQOL-5 Dimension-3 Level Scale, a Columbia-Suicide Severity Rating Scale, a Suicidal Ideation Attributes Scale, or any combinations thereof.

13. The method of embodiment 10, wherein the functional MRI measures the amygdala blood oxygen level-dependent (BOLD) response.

14. The method of embodiment 13, wherein the BOLD response is measured at resting state, in response to emotional faces, and/or music as a hedonic stimulus.

15. The method of any one of embodiments 1-14, wherein at least one sign or symptom of depression is alleviated within 24 hours of administration of the psilocybin.

16. The method of any one of embodiments 1-14, wherein at least one symptom of depression is alleviated within 1 week of administration of the psilocybin.

17. The method of any one of embodiments 1-14, wherein at least one symptom of depression is alleviated for a period of at least 1 month after administration of the psilocybin.

18. The method of any one of embodiments 1-14, wherein the at least one symptom of depression is alleviated for a period of at least 3 months after administration of the psilocybin.

19. The method of any one of embodiments 1-14, wherein the at least one symptom of depression is alleviated for a period of at least 12 months after administration of the psilocybin.

20. The method of any one of embodiments 1-19, wherein no other treatment is administered to the subject to reduce the sign or symptom of depression after administration of the psilocybin.

21. The method of any one of embodiments 1-19, wherein the method further comprises administering to the subject at least one additional therapeutic to reduce the sign or symptom of depression.

22. The method of embodiment 21, wherein the at least one additional therapeutic is selective serotonin reuptake inhibitor, a serotonin and norepinephrine reuptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, a dopamine reuptake inhibitor, a 5-HT1A receptor

antagonist, a 5-HT2 receptor antagonist, a 5-HT3 receptor antagonist, a monoamine oxidase inhibitor, or a noradrenergic antagonist.

23. The method of embodiment 21 or 22, wherein the at least one additional therapeutic is administered prior to administration of psilocybin.

24. The method of embodiment 21 or 22, wherein the at least one additional therapeutic is administered after administration of psilocybin.

25. The method of embodiment 21 or 22, wherein the at least one additional therapeutic is administered on the same day as the psilocybin.

26. The method of any one of embodiments 1-25, wherein the subject has no prior psilocybin exposure.

27. The method of any one of embodiments 1-25, wherein the subject has prior psilocybin exposure.

28. The method of any one of embodiments 1-27, wherein the subject has an additional comorbidity or disorder.

29. The method of embodiment 28, wherein the subject has an anxiety disorder, an obsessive-compulsive disorder, alcoholism, a personality disorder, a cardiovascular disease, a neurological disease, or cancer.

30. The method of embodiment 29, wherein the neurological disease is dementia, Alzheimer's Disease, or Parkinson's Disease.

31. The method of any one of embodiments 28-30, wherein reducing at least one sign or symptom of depression in the subject treats or prevents one or more comorbidities or disorders in the subject.

32. The method of any one of embodiments 1-31, wherein the subject is a mammal.

33. The method of embodiment 32, wherein the subject is human.

34. The method of any of embodiments 1-33, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin comprises at least 90% by weight of Polymorph A.

35. The method of embodiment 34, wherein the crystalline psilocybin comprises at least 95% by weight of Polymorph A.

36. The method of embodiment 34 or 35, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

37. The method of any one of embodiments 1-33, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin

in the form of Polymorph A, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

38. The method of embodiment 37, wherein the highly pure crystalline psilocybin comprises at least 90% by weight of Polymorph A.

39. The method of embodiment 38, wherein the highly pure crystalline psilocybin comprises at least 95% by weight of Polymorph A.

40. The method of any one of embodiments 34-39, wherein the highly pure crystalline psilocybin is further characterized having either: (i) a water content of <0.5% w/w; or (ii) <0.5% w/w loss in the TGA thermogram between 25° C and 200° C.

41. The method of any one of embodiments 34-40, wherein the highly pure crystalline psilocybin is further characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 155°C and a second onset temperature of between 205 and 220°C.

42. The method of any one of embodiments 34-41, wherein the highly pure crystalline psilocybin is further characterized by one or more of the following: (a) a loss on drying of no more than 2% w/w; (b) residue on ignition of no more than 0.5% w/w; (c) assay (on a dry basis) of 95-103% by weight as measured by HPLC; (d) residual solvent content of no more than 3000 ppm methanol; 5000 ppm ethanol, 720 ppm THF, and 890 ppm toluene, as measured by HRGC; (e) phosphoric acid content of no more than 1% w/w as measured by ^{31}P NMR; and (f) Inductively Coupled Plasma Mass Spectrometry (ICP-MS) elemental analysis of: (i) no more than 1.5ppm Cd; (ii) no more than 1.5ppm Pb; (iii) no more than 4.5ppm As; (iv) no more than 9.0ppm Hg; (v) no more than 15ppm Co; (vi) no more than 30ppm V; (vii) no more than 60ppm Ni; (viii) no more than 165ppm Li; and (ix) no more than 30ppm Pd.

43. The method of any one of embodiments 34-42, wherein the highly pure crystalline psilocybin has no single impurity of greater than 0.5%.

44. The method of any of embodiments 34-43, wherein the dosage form further comprises about 5 to 40 mg of the highly pure crystalline psilocybin.

45. The method of embodiment 44, wherein the dosage form comprises 5 mg of highly pure crystalline psilocybin.

46. The method of embodiment 44, wherein the dosage form comprises about 10 mg of highly pure crystalline psilocybin.

47. The method of embodiment 44, wherein the dosage form comprises about 35 mg of highly pure crystalline psilocybin.

48. The method of any one of embodiments 34-47, wherein the dosage form comprises silicified microcrystalline cellulose.

49. The method of embodiment 48, wherein the silicified microcrystalline cellulose has a particle size range from about 45 to 150 microns.

50. The method of any one of embodiments 34-49, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns and the second variant has a particle size of about 90 to 150 microns.

51. The method of embodiment 50, wherein about 30% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 70% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

52. The method of embodiment 50, wherein about 20% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 80% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

53. The method of embodiment 50, wherein about 15% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 85% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

54. The method of embodiment 53, wherein the dosage form comprises 5 mg of crystalline psilocybin in the form of Polymorph A, 12.5 mg of SMCC 50, 79.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide and 1 mg sodium stearyl fumarate.

55. The method of embodiment 53, wherein the dosage form comprises 1 mg of crystalline psilocybin in the form of Polymorph A, 20.5 mg of SMCC 50, 75.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide, and 1 mg sodium stearyl fumarate.

56. The method of any one of embodiments 34-55, wherein the dosage form is an oral dosage form.

57. The method of embodiment 56, wherein the dosage form is a capsule.

58. The method of embodiment 56, wherein the dosage form is a tablet.

59. The method of any one of embodiments 1-58, wherein at least one dose of psilocybin is administered to the subject.

60. The method of embodiment 59, wherein the at least onedose of psilocybin is in the range of about 0.1 mg to about 100 mg.

61. The method of embodiment 60, wherein the dose of psilocybin is about 1 mg.

62. The method of embodiment 60, wherein the dose of psilocybin is about 10 mg.

63. The method of embodiment 60, wherein the dose of psilocybin is about 25 mg.

64. The method of any one of embodiments 1-58, wherein more than one dose of psilocybin is administered to the subject.

65. The method of embodiment 65, wherein at least two doses of psilocybin are administered to the subject.

66. The method of any one of embodiments 64-65, wherein the psilocybin is administered once per day.

67. The method of any one of embodiments 64-65, wherein the psilocybin is administered at least once per week.

68. The method of any one of embodiments 64-65, wherein the psilocybin is administered at least twice per week.

69. The method of any one of embodiments 64-65, wherein the psilocybin is administered at least once per month.

70. The method of any one of embodiments 64-65, wherein the psilocybin is administered at least twice per month.

71. The method of any one of embodiments 64-65, wherein the psilocybin is administered at least once every three months.

72. The method of any one of embodiments 64-65, wherein the psilocybin is administered at least once every six months.

73. The method of any one of embodiments 64-65, wherein the psilocybin is administered at least once every 12 months.

74. The method of any one of embodiments 64-73, wherein each dose of psilocybin administered is in the range of about 0.1 mg to about 100 mg.

75. The method of embodiment 74, wherein each dose of psilocybin administered is about 1 mg.

76. The method of embodiment 74, wherein each dose of psilocybin administered is about 10 mg.

77. The method of embodiment 74, wherein each dose of psilocybin administered is about 25 mg.

78. The method of any one of embodiments 59-77, wherein the psilocybin is administered by one of the following routes: oral, intravenous, intramuscular, parenteral, topical, inhalation, rectal, transmucosal, intranasal, buccal, vaginal, intrathecal, intraocular, transdermal, in utero, intralymphatic, or by direct tissue or organ injection.

79. The method of embodiment 78, wherein the psilocybin is administered orally.

80. The method of any one of embodiments 1-79, wherein the subject participates in at least one psychological support session before administration of the psilocybin.

81. The method of embodiment 80, wherein the subject participates in at least three psychological support sessions before administration of the psilocybin.

82. The method of any one of embodiments 80-81, wherein the at least one therapeutic intention is discussed during the psychological support session.

83. The method of any one of embodiments 80-82, wherein self-directed inquiry and experiential processing are practiced during the psychological support session.

84. The method of any one of embodiments 80-83, wherein the subject participates in at least one psychological support session after administration of the psilocybin.

85. The method of embodiment 84, wherein the subject participates in at least three psychological support sessions after administration of the psilocybin.

86. The method of any one of embodiments 80-85, wherein the psilocybin is administered to the subject in a room with a substantially non-clinical appearance.

87. The method of embodiment 86, wherein the room comprises soft furniture.

88. The method of embodiment 86, wherein the room is decorated using muted colors.

89. The method of embodiment 86, wherein the room comprises a high-resolution sound system.

90. The method of any one of embodiments 86-89, wherein the room comprises a bed or a couch.

91. The method of embodiment 90, wherein the subject lies in the bed or on the couch for approximately 4-8 hours, or a substantial fraction thereof, after administration of the psilocybin.

92. The method of any one of embodiments 86-91, wherein the subject listens to music for approximately 4-8 hours, ora substantial fraction thereof, after administration of the psilocybin.

93. The method of any one of embodiments 86-92, wherein the subject wears an eye mask for approximately 4-8 hours, or a substantial fraction thereof, after administration of the psilocybin.

94. The method of any one of embodiments 87-93, wherein a therapist provides psychological support to the subject for approximately 4-8 hours after administration of the psilocybin.

95. The method of embodiment 94, wherein the therapist uses guided imagery and/or breathing exercises to calm the subject and/or focus the subject's attention.

96. The method of embodiment 94, wherein the therapist provides reassuring physical contact with the subject.

97. The method of embodiment 96, wherein the therapist holds the hand, arm, or shoulder of the subject.

98. The method of embodiment 94, wherein the therapist encourages the subject to perform self-directed inquiry and experiential processing.

99. The method of embodiment 94, wherein the therapist reminds the subject of at least one therapeutic intention.

100. The method of embodiment 94, wherein the therapist counsels the subject to do one or more of the following: (1) to accept feelings of anxiety, (2) to allow the experience to unfold naturally, (3) to avoid psychologically resisting the experience, (4) to relax, and/or (5) to explore the subject's own mental space.

101 . The method of embodiment 94, wherein the therapist does not initiate conversation with the subject.

102. The method of embodiment 94, wherein the therapist responds to the subject if the subject initiates conversation.

103. The method of any one of embodiments 80-102, wherein the psychological support is provided remotely to the subject.

104. The method of embodiment 103, wherein the psychological support is provided via a digital or electronic system.

105. The method of embodiment 104, wherein the digital or electronic system is a mobile phone app.

106. The method of embodiment 105, wherein the digital or electronic system is a website.

107. A method as described herein.

108. A formulation as described herein.

109. Crystalline psilocybin as described herein.

Numbered Embodiments for Co-Administration of Psilocybin and Benzodiazepines

1. A method of reducing anxiety in a subject undergoing treatment with psilocybin, the method comprising administering to the subject:

i) psilocybin or a precursor or derivative thereof, and

ii) one or more benzodiazepines.

2. The method of embodiment 1, wherein the subject suffers from a disease, disorder, or condition selected from Disruptive Mood Dysregulation Disorder, Major Depressive Disorder

(MDD), Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, and Kleptomania.

3. The method of embodiment 1 or 2, wherein the one or more benzodiazepines are administered to the subject at or around the same time as the psilocybin or precursor or derivative thereof.

4. The method of embodiment 1 or 2, wherein the one or more benzodiazepines are administered to the subject prior to administration of the psilocybin or precursor or derivative thereof.

5. The method of embodiment 4, wherein the one or more benzodiazepines are administered to the subject about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes before administration of the psilocybin or precursor or derivative thereof.

6. The method of embodiment 1 or 2, wherein the one or more benzodiazepines are administered to the subject after the psilocybin or precursor or derivative thereof.

7. The method of embodiment 6, wherein the one or more benzodiazepines are administered to the subject about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes after administration of the psilocybin or precursor or derivative thereof.

8. The method of any one of embodiments 1-7, wherein the psilocybin or precursor or derivative thereof, is administered to the subject at a dose of between about 0.1 mg to about 100 mg.

9. The method of embodiment 8, wherein the psilocybin or precursor or derivative thereof is administered to the subject at a dose of between about 1 mg to about 50 mg.

10. The method of embodiment 9, wherein the psilocybin or precursor or derivative thereof is administered to the subject at a dose of about 1 mg, about 10 mg, or about 25 mg.

11. The method of any one of embodiments 1-10, wherein the one or more benzodiazepines are administered at a dose that is lower than doses typically used to treat anxiety.

12. The method of embodiment 11, wherein the dose is about 10%, 20%, 25%, 30%, 40%, 50%, or 75% of a typical dose.

13. The method of any one of embodiments 1-10, wherein the one or more benzodiazepines are administered at a dose that is approximately equivalent to doses typically used to treat anxiety.

14. The method of any one of embodiments 1-10, wherein the one or more benzodiazepines are administered at a dose that is higher than doses typically used to treat anxiety.

15. The method of embodiment 14, wherein the dose is about 125%, 150%, 175%, 200%, 250%, or 300% of a typical dose.

16. The method of any one of embodiments 1-15, wherein the benzodiazepine is selected from the group consisting of adinazolam, alprazolam, bentazepam, bretazenil, bromazepam, bromazolam, brotizolam .camazepam, chlordiazepoxide, cinazepam, cinolazepam, clobazam, clonazepam, clonazolam, clorazepate, clotiazepam, cloxazolam, delorazepam, deschloroetizolam, diazepam, diclazepam, estazolam, ethyl carfluzepate, ethyl loflazepate, etizolam, flualprazolam, flubromazepam, flubromazolam, fluclotizolam, flunitrazepam, flunitrazolam, flurazepam, flutazolam, flutoprazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, meclonazepam, medazepam, metizolam, mexazolam, midazolam, nifoxipam, nimetazepam, nitemazepam, nitrazepam, nitrazolam, nordiazepam, norflurazepam, oxazepam, phenazepam, pinazepam, prazepam, premazepam, pyrazolam, quazepam, rilmazafone, temazepam, tetrazepam, and triazolam.

17. The method of embodiment 16, wherein the benzodiazepine is alprazolam.

18. The method of embodiment 16, wherein the benzodiazepine is diazepam.

19. The method of any one of embodiments 1-18, wherein the psilocybin is a crystalline psilocybin in the form of Polymorph A, Polymorph A', Polymorph B, or Hydrate A.

20. The method of embodiment 19, wherein the crystalline psilocybin is Polymorph A, characterised by one or more of:

a. peaks in an XRPD diffractogram at 11.5, 12.0,14.5, and 17.5, °2Θ±0.1 °2Θ;

b. peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5, °2Θ±0.1 °2Θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1°2Θ;

c. an XRPD diffractogram as substantially illustrated in Figure 2a; and/or

d. an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in Figure 3a.

21. The method of embodiment 19, wherein the crystalline psilocybin is Polymorph A', characterised by one or more of:

a. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °20±0. 1°2θ;

b. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °2Θ±0.1 °2Θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ;

c. an XRPD diffractogram as substantially illustrated in Figure 2b; and/or

d. an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in Figure 3b.

22. The method of any one of embodiments 1-21, wherein the psilocybin or precursor or derivative thereof is administered orally to the subject.

23. The method of any one of embodiments 1-22, wherein the one or more benzodiazepine is administered orally to the subject.

24. The method of any one of embodiments 1-23, wherein the psilocybin or precursor or derivative thereof is administered at least once to the subject.

25. The method of embodiment 24, wherein the psilocybin is administered at least twice to the subject, at therapeutically effective intervals.

26. The method of embodiment 25, wherein the therapeutically effective intervals are about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, or about 12 weeks.

27. The method of any one of embodiments 1-16, wherein the subject has never taken psilocybin before.

28. The method of any one of embodiments 1-26, wherein the subject has taken psilocybin before.

29. The method of any one of embodiments 1-28, wherein the subject is supervised during the administration and for at least 4 to 12 hours thereafter.

30. The method of any one of embodiments 1-29, wherein the subject receives psychological support during the administration, and for at least 4 to 12 hours thereafter.

31. The method of any one of embodiments 1-30, wherein the subject has not taken any serotonergic antidepressant for at least 2 weeks, at least 4 weeks, or at least 6 weeks prior.

32. The method of any one of embodiments 1-31, wherein the subject receives counseling with regard to the expected effects of the psilocybin.

33. The method of any one of embodiments 1-32, wherein the subject is a male.

34. The method of any one of embodiments 1-32, wherein the subject is a female.

35. A combination therapy for treating or preventing a disease, disorder, or condition selected from Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Distorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-

Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, and Kleptomania, the combination therapy comprising administering to the subject:

i) psilocybin or a precursor or derivative thereof, and

ii) one or more benzodiazepines.

36. A kit for treating a subject in need thereof, the kit comprising:

a first pharmaceutical composition comprising psilocybin, or a precursor or derivative thereof, and

a second pharmaceutical composition comprising one or more benzodiazepines.

37. The kit of embodiment 36, wherein the kit further comprises instructions for administering the first and the second pharmaceutical composition to the subject.

Numbered Embodiments for Co-Administration of Psilocybin and 5-HT2A Specific Antagonists and/or Inverse Agonists.

1. A method of reducing the negative side effects associated with a traumatic psychedelic experience in a subject undergoing treatment with psilocybin, the method comprising administering to the subject:

i) psilocybin or a precursor or derivative thereof, and

ii) one or more 5-HT_{2A} specific antagonists and/or inverse agonists.

2. The method of embodiment 1, wherein the subject suffers from a disease, disorder, or condition selected from Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder,

Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, Kleptomania, and burnout, vegetative states, and asthma (and other inflammatory diseases).

3. The method of embodiment 1 or 2, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered to the subject at or around the same time as the psilocybin or precursor or derivative thereof.

4. The method of embodiment 1 or 2, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered to the subject prior to administration of the psilocybin or precursor or derivative thereof.

5. The method of embodiment 4, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered to the subject about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes before administration of the psilocybin or precursor or derivative thereof.

6. The method of embodiment 1 or 2, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered to the subject after the psilocybin or precursor or derivative thereof.

7. The method of embodiment 6, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered to the subject about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, about 90 minutes, about 105 minutes, about 120 minutes, about 150 minutes, or about 180 minutes after administration of the psilocybin or precursor or derivative thereof.

8. The method of any one of embodiments 1-7, wherein the psilocybin or precursor or derivative thereof, is administered to the subject at a dose of between about 0.1 mg to about 100 mg.

9. The method of embodiment 8, wherein the psilocybin or precursor or derivative thereof is administered to the subject at a dose of between about 1 mg to about 50 mg.

10. The method of embodiment 9, wherein the psilocybin or precursor or derivative thereof is administered to the subject at a dose of about 1 mg, about 10 mg, or about 25 mg.

11. The method of any one of embodiments 1-10, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered at a dose that is lower than a typical dose.

12. The method of embodiment 11, wherein the dose is about 10%, 20%, 25%, 30%, 40%, 50%, or 75% of a typical dose.

13. The method of any one of embodiments 1-10, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered at a dose that is approximately equivalent to a typical dose.

14. The method of any one of embodiments 1-10, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists are administered at a dose that is higher than a typical dose.

15. The method of embodiment 14, wherein the dose is about 125%, 150%, 175%, 200%, 250%, or 300% of a typical dose.

16. The method of any one of embodiments 1-15, wherein the 5-HT_{2A} specific antagonist is trazodone, mirtazapine, metergoline, ketanserin, ritanserin, nefazodone, clozapine, olanzapine, quetiapine, risperidone, asenapine, MDL-1 00907, cyproheptadine, pizotifen, LY-367,265, 2-alkyl-4-aryl-tetrahydro-pyrimido-azepine, 9-aminomethyl-9,10-dihydroanthracene (AMDA), haloperidol, chlorpromazine, hydroxyzine (atarax), 5-MeO-NBpBrT, niaprazine, altanserin, aripiprazole, etoperidone, setoperone, chlorprothixene, cinaserin, adatanserin, medifoxamine, rauwolscine, phenoxybenzamine, pruvanserin, deramciclane, nelotanserin, lubazodone, mepiprazole, xylamidine, R-(+)-alpha-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenethyl)]-4-piperidinemethanol (M100907), mianserin, AT 1015, DV 7028, eplivanserin, 4F 4PP, fanaserin, alpha-phenyl-1-(2-phenylethyl)-4-piperidinemethanol (MDL 11,939), melperone, mesulergine, paliperidone, 1-[2-(3,4-Dihydro-1 H-2-benzopyran-1 -yl)ethyl]-4-(4-fluorophenyl)piperazine dihydrochloride (PNU 9641 5E), (2R,4R)-5-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-3-pyrrolidinol (R-96544), sarpogrelate, spiperone, ziprasidone, zotepine, or 7-[[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]carbonyl]-1 H-indole-3-carbonitrile (EMD 281014).

17. The method of embodiment 16, wherein the 5-HT_{2A} specific antagonist is ketanserin..

18. The method of any one of embodiments 1-15, wherein the 5-HT_{2A} inverse antagonist is AC-90179, nelotanserin (APD-125), eplivanserin, pimavanserin (ACP-103), or volinaserin.

19. The method of embodiment 18, wherein the 5-HT_{2A} inverse antagonist is pimavanserin.

20. The method of any one of embodiments 1-19, wherein the psilocybin is a crystalline psilocybin in the form of Polymorph A, Polymorph A', Polymorph B, or Hydrate A.

21. The method of embodiment 20, wherein the crystalline psilocybin is Polymorph A, characterised by one or more of:

e. peaks in an XRPD diffractogram at 11.5, 12.0,14.5, and 17.5, °2Θ±0.1 °2Θ;

f. peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5, °2Θ±0.1 °2Θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1°2Θ;

g. an XRPD diffractogram as substantially illustrated in Figure 2a; and/or

h. an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in Figure 3a.

22. The method of embodiment 20, wherein the crystalline psilocybin is Polymorph A', characterised by one or more of:

e. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °20±0. 1°2θ;

f. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °2Θ±0.1 °2Θ, further characterised by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ;

g. an XRPD diffractogram as substantially illustrated in Figure 2b; and/or

h. an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in Figure 3b.

23. The method of any one of embodiments 1-22, wherein the psilocybin or precursor or derivative thereof is administered orally to the subject.

24. The method of any one of embodiments 1-23, wherein the one or more 5-HT_{2A} specific antagonists and/or inverse agonists is administered orally to the subject.

25. The method of any one of embodiments 1-24, wherein the psilocybin or precursor or derivative thereof is administered at least once to the subject.

26. The method of embodiment 25, wherein the psilocybin is administered at least twice to the subject, at therapeutically effective intervals.

27. The method of embodiment 26, wherein the therapeutically effective intervals are about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, or about 12 weeks.

28. The method of any one of embodiments 1-27, wherein the subject has never taken psilocybin before.

29. The method of any one of embodiments 1-27, wherein the subject has taken psilocybin before.

30. The method of any one of embodiments 1-29, wherein the subject is supervised during the administration and for at least 4 to 12 hours thereafter.

31. The method of any one of embodiments 1-30, wherein the subject receives psychological support during the administration, and for at least 4 to 12 hours thereafter.

32. The method of any one of embodiments 1-31, wherein the subject has not taken any serotonergic antidepressant for at least 2 weeks, at least 4 weeks, or at least 6 weeks prior.

33. The method of any one of embodiments 1-32, wherein the subject receives counseling with regard to the expected effects of the psilocybin.

34. The method of any one of embodiments 1-33, wherein the subject is a male.

35. The method of any one of embodiments 1-33, wherein the subject is a female.

36. A combination therapy for treating or preventing a disease, disorder, or condition selected from Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Distorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder,

Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, Kleptomania, and burnout, vegetative states, and asthma (and other inflammatory diseases), the combination therapy comprising administering to the subject:

i) psilocybin or a precursor or derivative thereof, and

ii) one or more 5-HT_{2A} specific antagonists and/or inverse agonists.

37. A kit for treating a subject in need thereof, the kit comprising:

a first pharmaceutical composition comprising psilocybin, or a precursor or derivative thereof, and

a second pharmaceutical composition comprising one or more 5-HT_{2A} specific antagonists and/or inverse agonists.

38. The kit of embodiment 37, wherein the kit further comprises instructions for administering the first and the second pharmaceutical composition to the subject.

39. A method of reducing the negative side effects associated with a traumatic psychedelic experience in a subject undergoing treatment with psilocybin, the method comprising administering to the subject:

i) psilocybin or a precursor or derivative thereof, and

ii) one or more cannabinoids or cannabinoid derivatives.

Numbered Embodiments related to Polymorph A and use thereof

1. Crystalline psilocybin Polymorph A or Polymorph A', characterised by one or more of:

a) peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, and/ or

b) an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 155°C and a second onset temperature of between 210°C and 220°C

for use in the treatment of: Alzheimer's, Autism spectrum disorder, Attention deficit hyperactivity disorder (ADHD), Downs, Epilepsy (though not seizures), Multiple Sclerosis, Parkinson's disease, Schizophrenia, Huntington's, Stroke and other cerebrovascular conditions, Traumatic brain injury, Major depressive disorder, chronic cluster headaches, antisocial personality disorder and psychopathy.

2. A method for the treatment of Alzheimer's, Autism spectrum disorder, Attention deficit hyperactivity disorder (ADHD), Downs, Epilepsy (though not seizures), Multiple Sclerosis, Parkinson's disease, Schizophrenia, Huntington's, Stroke and other cerebrovascular conditions, Traumatic brain injury, Major depressive disorder, chronic cluster headaches, antisocial personality disorder and psychopathy comprising administering to a subject in need thereof an

effective amount of crystalline psilocybin Polymorph A or Polymorph A', characterised by one or more of

a) peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ; and/ or

b) an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 155°C and a second onset temperature of between 210°C and 220°C.

3. Crystalline psilocybin Polymorph A or Polymorph A', characterised by one or more of:

a) peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ; and/ or

b) an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 155°C and a second onset temperature of between 210°C and 220°C

for use in the treatment of a central nervous disorder together with psychotherapy wherein the psychotherapy is a transdiagnostic therapy.

4. Crystalline psilocybin Polymorph A or Polymorph A' for use as claimed in claim 3 wherein the transdiagnostic therapy is a Method of Levels (MOL) therapy.

5. Crystalline psilocybin Polymorph A or Polymorph A' for use as claimed in claim 4 wherein the Method of Levels (MOL) therapy comprises Self-directed enquiry and Experiential processing.

6. A method for the treatment of a central nervous disorder together with psychotherapy wherein the psychotherapy is a transdiagnostic therapy.

7. A method as claimed in claim 6 wherein the transdiagnostic therapy is a Method of Levels (MOL) therapy.

8. A method as claimed in claim 7 wherein the Method of Levels (MOL) therapy comprises Self-directed enquiry and Experiential processing.

9. A digital biomarker, as a diagnostic and / or prognostic tool for patient management pre, during and/ or post treatment of a central nervous system disorder with psilocybin wherein the digital biomarker is one or more biomarkers associated with executive function, cognitive control, working memory, processing speed, and emotional valence.

10. A digital biomarker as claimed in claim 9 wherein the biomarker is identified from patterns in smartphone use such as swipes, taps, and other touchscreen activities, and are scientifically validated to provide measurements of cognition and mood.

11. A digital biomarker as claimed in claim 10 wherein the pattern is identified using one or more:

Number of and/ or time of phone calls/e-mails/texts;

Gestures used (taps, swipes, or other);

Gyroscope derived information e.g. orientation of the phone;

Acceleration of the phone;

Keystroke patterns;

Location derived information from GPS; and / or

Specific words or emojis used or not used;

and the central nervous system disorder treated is treatment resistant depression.

12. A method of assessing a subject pre, during and/ or post treatment of a central nervous system disorder to determine whether to provide a psilocybin treatment or a further psilocybin treatment comprising monitoring one or more biomarkers associated with executive function, cognitive control, working memory, processing speed, and emotional valence, and determining the treatment based on an outcome.

13. A method as claimed in claim 12 further comprising administering psilocybin for a first or a subsequent time.

14. A method as claimed in claim 13 wherein the psilocybin is administered together with psychotherapy.

Numbered embodiment for formulations of psilocybin

1. A pharmaceutic formulation comprising psilocybin, one or more fillers, and one or more disintegrants.

2. The pharmaceutical formulation of embodiment 1 wherein one or more of the fillers is a silicified filler.

3. The pharmaceutical formulation of embodiment 2 wherein one or more silicified filler is silicified microcrystalline cellulose.

4. The pharmaceutical formulation of embodiment 3 comprising silicified microcrystalline cellulose with a particle size range of from about 45 to 80 microns (SMCC 50), silicified microcrystalline cellulose with a particle size range of from about 90 to 150 microns (SMCC 90), or mixtures thereof.

5. The pharmaceutical formulation of embodiment 4 comprising SMCC 50 and SMCC 90.

6. The pharmaceutical formulation of embodiment 5 wherein the ratio of SMCC 50 to SMCC 90 is 1:5 to 1:8 (SMCC 50: SMCC 90) wt %.

7. The pharmaceutical formulation of embodiment 6 wherein the ratio of SMCC 50 to SMCC 90 is 1:6 to 1:7(SMCC 50: SMCC 90) wt %.

8. The pharmaceutical formulation of embodiment 7 wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 (SMCC 50: SMCC 90) wt %.

9. The pharmaceutical formulation of any of embodiment 1-8 wherein the disintegrant is present in an amount of less than 3% by weight.

10. The pharmaceutical formulation of embodiment 9 wherein the disintegrant is present in an amount of less than 2% by weight.

11. The pharmaceutical formulation of embodiment 10 wherein the disintegrant is present in an amount of 1% or less by weight.

12. The pharmaceutical formulation of any of embodiment 1-1 1 wherein the disintegrant is sodium starch glycolate, croscarmellose sodium, or mixtures thereof.

13. The pharmaceutical formulation of embodiment 12 wherein the disintegrant is sodium starch glycolate.

14. The pharmaceutical formulation of any of embodiment 1-13 wherein the psilocybin is crystalline psilocybin in the form of Polymorph A, Polymorph A', Polymorph B, or Hydrate A.

15. The pharmaceutical formulation of embodiment 14 wherein the psilocybin is crystalline psilocybin in the form of Polymorph A, characterized by one or more of:

a. peaks in an XRPD diffractogram at 11.5, 12.0,14.5, and 17.5, °2Θ±0.1 °2Θ;

b. peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5, °2Θ±0.1 °2Θ, further characterized by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ;

c. an XRPD diffractogram as substantially illustrated in Figure 7a; and/or

d. an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in Figure 8a.

16. The pharmaceutical formulation of embodiment 14 wherein the psilocybin is crystalline psilocybin in the form of Polymorph A', according to embodiment 1 or 2 characterized by one or more of:

a. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °2Θ±0.1 °2Θ;

b. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ, but absent or substantially absent of a peak at 17.5 °2Θ±0.1°2Θ, further characterized by at least one further peak at 19.7, 20.4, 22.2, 24.3 or 25.7 °2Θ±0.1 °2Θ;

c. an XRPD diffractogram as substantially illustrated in Figure 7b; and/or

d. an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C substantially as illustrated in Figure 8b.

17. The pharmaceutical formulation of any of embodiment 1-16 comprising about 1 mg to about 50 mg psilocybin.

18. The pharmaceutical formulation of embodiment 17 comprising about 1mg, 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg, or 50mg psilocybin.

19. A method for large scale manufacture of psilocybin in the form Polymorph A or Polymorph A', characterised by one or more of

a) peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5 °2Θ±0.1 °2Θ; and/ or

b) an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 165°C and a second onset temperature of between 205°C and 220°C

wherein the method comprises water crystallization wherein psilocybin is solubilized in water at a temperature below 90 °C to provide an aqueous solution of psilocybin.

20. The method of embodiment 19 wherein psilocybin is solubilized in water at a temperature below 85 °C to provide an aqueous solution of psilocybin.

21. The method of embodiment 19 or 20 wherein the temperature of the aqueous solution of psilocybin is lowered at a rate of about 5 °C -15 °C an hour to provide crystalline psilocybin

22. The method of embodiment 21 wherein the temperature of the aqueous solution of psilocybin is lowered at a rate of about 10 °C an hour to provide crystalline psilocybin.

23. The method of any one of embodiments 19-22 further comprising stirring the solution during solubilization.

EXAMPLES

The following examples, which are included herein for illustration purposes only, are not intended to be limiting.

Example 1 – Formulation development.

The five formulations (Ex 1A, 1B, 1C, 1D, and 1E) described in Table 1A were assessed for powder flow, blend uniformity, content uniformity and dissolution.

Table 1A

Material Name	% w/w				
	Ex 1A	Ex 1B	Ex 1C	Ex 1D	Ex 1E
Psilocybin	1.0	1.0	1.0	1.0	1.0
Prosolv SMCC 50*	15.5	20.5	10.5	20.5	10.5
Prosolv SMCC 90*	79.0	74.0	83.5	73.5	84.25
Ratio	1:5.1	1:3.6	1:8	1:3.6	1:8
Sodium Starch glycolate	3.0	3.0	3.0	3.0	3.0

Colloidal Silicon Dioxide (Aerosil 200)	0.5	0.25	1.0	1.0	0.25
Sodium Stearyl Fumarate	1.0	1.0	1.0	1.0	1.0
TOTAL weight of tablet	100.0	100.0	100.0	100.0	100.0
Powder flow (Hausner ratio)	22.4	26.5	21.8	21.3	19.5
Blend Uniformity					
TOP	107.6	103.0	96.0	97.0	96.0
MIDDLE	114.3	106.9	100.0	99.0	99.0
BOTTOM	125.6	109.3	108.0	104.0	103.0
MEAN	115.8	106.4	101.0	100.0	99.0
% RSD	7.8	3.7	5.5	3.3	3.1
Content Uniformity					
% label Claim	97.0	96.0	95.0	98.0	96.0
AV	4.3	4.5	5.5	2.0	4.8
Dissolution Time (min)	% release				
5	94	93	92	94	94
10	96	96	95	97	96
15	96	96	95	97	95
30	95	96	95	96	95
Infinity	95	95	94	96	94
Assay (%)					
	97.0	95.0	95.0	98.0	96.0

*The quantity of fillers adjusted to account for glidant quantity and total tablet weight.

Ex. 1D was used as a base formulation for the optimization of an exemplary higher dose tablet (5 mg). Tablets tested for dissolution from all five examples were found be unaffected by change in the fillers ratio and quantity of glidant. Hence, it was decided to study the level of disintegrate in the final formulation. Two batches of Psilocybin tablet 5 mg were manufactured using high (3% w/w) and low (1% w/w) levels of a disintegrant in the formulation composition.

The additional studies were conducted to justify the amount of disintegrant in the formulation. These studies were performed on the higher strength product (5 mg).

A quantity of fillerwas replaced with psilocybin, the active pharmaceutical ingredient (API) in order to accommodate the additional amount API. The formulation composition and results for powder flow, blend uniformity, content uniformity and dissolution for Ex. 1F and 1G are summarized in Table 1B.

Table 1B

Material Name	% w/w	
	Ex. 1F	Ex. 1G
Psilocybin	5.0	5.0
Prosolv SMCC 50	14.5	12.5
Prosolv SMCC 90	75.5	79.5
Ratio	1:5.2	1:6.4
Sodium Starch glycolate	3.0	1.0
Colloidal Silicon Dioxide (Aerosil 200)	1.0	1.0
Sodium Stearyl Fumarate	1.0	1.0
TOTAL weight of tablet	100.0	100.0
Powder flow (Hausner ratio)	22.6	20.9
Blend Uniformity		
TOP	98.0	98.0
MIDDLE	99.0	99.0
BOTTOM	102.0	100.0
MEAN	100.0	99.0
% RSD	1.7	1.9
Content Uniformity		
% label Claim	96.0	97.0
AV	9.2	3.7
Dissolution Time (min)	% release	
5	98.0	90.0
10	101.0	102.0
15	100.0	102.0

30	100.0	101.0
Infinity	99.0	101.0
Assay (%)		
	96.0	97.0

Both examples met pre-defined criteria for blend uniformity, content uniformity, assay and dissolution. The material flow property was measured using Hausner ratio and no significant difference was found between the two formulations. However, the content uniformity results for Ex. 1G (AV=3.7) was found better in comparison to Ex. 1F (AV=9.2).

Tablets from both batches (Ex. 1F and Ex. 1G) were tested for dissolution. The results showed no significant difference between two formulations.

Psilocybin tablet formulations comprising 1 mg and 5 mg of API are presented in Table 1C.

Table 1C

Excipient/ material Name	Psilocybin 1 mg Tablet		Psilocybin 5 mg Tablet	
	Percent Formula (% w/w)	Quantity (mg/tablet)	Percent Formula (% w/w)	Quantity (mg/tablet)
Psilocybin	1.0	1.0	5.0	5.0
Silicified Microcrystaline Cellulose SMCC 50	20.5	20.5	12.5	12.5
Silicified Microcrystaline Cellulose SMCC 90	75.5	75.5	79.5	79.5
Ratio	1:3.7		1:6.4	
Sodium Starch Glycolate (disintegrant)	1.0	1.0	1.0	1.0
Colloidal silicon Dioxide (Aerosil)	1.0	1.0	1.0	1.0

(glidant)				
Sodium Stearyl Fumarate (Pruv) (lubricant)	1.0	1.0	1.0	1.0
TOTAL	100.0	100.0	100.0	100.0

It will be noted that alternative disintegrants, glidants and lubricants to those exemplified may be used.

Example 2: Treating a Subject with High Dose Psilocybin

Initially, a subject is counseled as to the expected effects of psilocybin by a professional who is trained to administer psilocybin therapy. One or more tablets or capsules comprising psilocybin are administered to the subject, in an environment where the subject is made to feel safe and comfortable. The total dose of psilocybin administered to the subject is between about 1 mg to about 25 mg.

The subject is supervised by the professional during administration of the psilocybin, and for a period of time thereafter *(e.g.,* from about 4 hours to about 12 hours) until the psychoactive effects of the psilocybin have worn off. Optionally, the subject may receive psychological support during administration of the psilocybin, and fora period of time thereafter (e.g., from about4 hours to about 12 hours).

Example 3: Safety and Efficacy of Psilocybin in Healthy Subjects

Aim of study:

A Phase 1 randomized, double-blind, placebo-controlled study to evaluate the effect of psilocybin on cognitive and emotional processing as compared to placebo in healthy volunteers was conducted. The study investigated the short-term (Day 7) and long-term (Day 28) effects of moderate (10 mg) and high doses (25 mg) of psilocybin on key domains of cognition, such as episodic memory, attention, working and spatial memory, social cognition and elements of executive function, including cognitive flexibility.

Study Design:

Subjects

90 healthy subjects were studied. Approximately 50% of the subjects were psilocybin-naive. For subjects with prior psilocybin experience, the last exposure was at least 1 year prior to the signing of the Informed Consent Form (ICF). Approximately 50% of the subjects were female. Subjects were stratified by sex and age (18-35 years old; > 35 years old).

Dosing Procedure:

Each subject was assigned 1 treatment bottle containing 5 capsules packaged in a double-blind fashion, depending on the randomized treatment arm, the bottle contained one of the following:

a. Psilocybin 10 mg: 2 × 5-mg oral psilocybin capsules plus 3 × placebo capsules
b. Psilocybin 25 mg: 5 χ 5-mg oral psilocybin capsules
c. Placebo: 5 x placebo capsules

Each 5-mg oral psilocybin capsules comprised 5 mg crystalline psilocybin in the form or Polymorph A, 12.5 mg of SMCC 50, 79.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide, and 1 mg sodium stearyl fumarate

The dose was swallowed with at least a full glass of water.

Outcome Measures:

The following list of outcome measures are non-exhaustive.

a. The short-term change from Baseline (Day -1 [Visit 2]) to Day 7 (Visit 5) in cognitive measures of attention, spatial and working memory and executive function was measured by a composite score of the CANTAB Panel (Spatial Working Memory [SWM], Rapid Visual Information Processing [RVP], Paired Associates Learning [PAL]).
b. The short-term change from Baseline (Day -1 [Visit 2]) to Day 7 (Visit 5) in Social Cognition Panel scales (Pictorial Empathy Test [PET], Reading the Mind in the Eyes Test [RMET], Toronto Empathy Questionnaire [TEQ], Social Value Orientation [SVO], Scale of Social Responsibility [SSR]).
c. The change from Baseline (Day -1 [Visit 2]) to Day 28 (Visit 6) in cognitive measures of attention, spatial and working memory and executive function as measured by a composite score of the CANTAB Panel (SWM, RVP, PAL).
d. The long-term change from Baseline (Day -1 [Visit 2]) to Day 84 (Visit 7) in Social Cognition Panel scales (PET, RMET, TEQ, SVO, SSR).
e. Dose-related differences between cognitive effects of psilocybin at Baseline (Day -1 [Visit 2]), Day 7 (Visit 5) and Day 28 (Visit 6), as measured by a composite score of the CANTAB Panel (SWM, RVP, PAL).
f. Dose-related differences between psychological effects of psilocybin at Baseline (Day -1 [Visit 2]), Day 7 (Visit 5) and Day 84 (Visit 7), as measured by Social Cognition Panel scales (PET, RMET, TEQ, SVO, SSR).

g. Differences in cognitive effects of psilocybin between psilocybin-naive and experienced subjects at Baseline (Day -1 [Visit 2]), Day 7 (Visit 5) and Day 28 (Visit 6), as measured by a composite score of the CANTAB Panel (SWM, RVP, PAL).

h. Differences in Positive and Negative Affect Schedule (PANAS) after study drug administration on Day 0 (Visit 3).

i. Differences between psilocybin and placebo in the Emotion Recognition Test (ERT), Intra-Extra Dimensional Set Shift (IED), One Touch Stockings (OTS), Verbal Fluency and Digit Span Forward at Day 7 (Visit 5).

j. A composite score of the CANTAB Panel, including the following tests:

   i. Spatial Working Memory (SWM) (performed at Visit 2, Visit 5, and Visit 6).

   ii. Rapid Visual Information Processing (RVP) (performed at Visit 2, Visit 5, and Visit 6).

   iii. Paired Associates Learning (PAL) (performed at Visit 2, Visit 5, and Visit 6).

k. Cognitive Flexibility Panel

   i. Emotion Recognition Task (ERT) (performed at Visit 5).

   ii. Intra-Extra Dimensional Set Shift (IED) (performed at Visit 5).

   iii. One Touch Stockings (OTS) (performed at Visit 5).

   iv. Verbal Fluency (performed at Visit 5).

   v. Digit Span Forward (performed at Visit 5).

l. Five Dimension Altered States of Consciousness questionnaire (5D-ASC) (performed at Visit 3).

m. PANAS (performed at Visit 2 and Visit 3).

n. NEO-Five Factor Inventory (NEO-FFI) (performed at Visit 2, Visit 5, and Visit 7).

o. Symptom Checklist-90 item (SCL-90) (performed at Visit 2, Visit 5, and Visit 7).

p. Life Changes Inventory (LCI): The LCI measures changes in attitudes and values after near-death experiences often used to evaluate personal transformation following spiritually oriented experiences and practices. (performed at Visit 5 and Visit 7).

q. Social Cognition Panel scales

   i. Pictorial Empathy Test (PET) (performed at Visit 2, Visit 5, and Visit 7).

ii. Reading the Mind in the Eyes Test (RMET) (performed at Visit 2, Visit 5, and Visit 7).

iii. Social Value Orientation (SVO) (performed at Visit 2, Visit 5, and Visit 7).

iv. Toronto Empathy Questionnaire (TEQ) (performed at Visit 2, Visit 5, and Visit 7).

v. Scale of Social Responsibility (SSR) (performed at Visit 2, Visit 5, and Visit 7).

r. Sheehan Suicidality Tracking Scale (SSTS)

s. Mini International Neuropsychiatric Interview (MINI).

t. McLean Screening Instrument for Borderline Personality Disorder (MSIBPD) (performed at Visit 1).

u. Tellegen Absorption Scale (performed at Visit 2).

v. Physical Examination (performed at Visit 1).

w. Electrocardiogram (ECG) (performed at Visit 1, Visit 2, Visit 3 and Visit 4).

Clinical Laboratory Tests: Blood samples were obtained at Screening (Visit 1) and Day 1 (Visit 4) for the following:

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

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

Urine samples were obtained at Screening (Visit 1) and Baseline (Visit 2) for the following:

i. Urine Drug Screen: for illicit drugs or drugs of abuse at Screening (Visit 1) and Baseline (Visit 2). Results of a positive drug screen will be reviewed by the study clinician for pattern of use.

ii. Urine Pregnancy Test: a dipstick test in females of childbearing potential at Screening (Visit 1) and Baseline (Visit 2).

Adverse events: Throughout the course of the study, all AEs were monitored and recorded. Each AE was classified according to the following criteria:

i. Mild: The AE does not interfere in a significant manner with the subject's normal level of functioning.

ii. Moderate: The AE produces some impairment of functioning, but is not hazardous to the subject's health.

iii. Severe: The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

Selected Adverse Events of included:

(a) Euphoric mood

(b) Dissociative disorder

(c) Hallucination

(d) Psychotic disorder

(e) Cognitive disorder

(f) Disturbance in attention

(g) Altered mood

(h) Impairment of psychomotor skills

(i) Inappropriate affect

(j) Overdose

(k) Intentional product misuse

(L) Illusion

Serious adverse events included:

(a) Death.

(b) Life-threatening: An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it did 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.

(c) Inpatient hospitalization or prolongation of existing hospitalization.

(d) Persistent or significant disability/incapacity.

(e) Congenital anomaly/birth defect in the offspring of a subject who received psilocybin.

(f) Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

(i) Intensive treatment in an emergency room or at home for allergic bronchospasm.

(ii) Blood dyscrasias or convulsions that do not result in inpatient hospitalization.

(iii) Development of drug dependency or drug abuse.

Visits:

Visit 1 (V1): Eligibility Screening (Days -56 to Day -2): All subjects were screened for eligibility in the 8 weeks (i.e., Day -56 to Day -2) prior to Baseline: including medical and psychiatric history, the Mini International Neuropsychiatric Interview (MINI, English version, 7.0.2), McLean Screening Instrument for Borderline Personality Disorder (MSIBPD), SSTS, physical examination, vital signs, body weight, height, body mass index (BMI), 12-lead electrocardiogram (ECG), clinical laboratory tests, urine drug screen, urine pregnancy test, documentation of contraceptive method, review of prior and concomitant medications and recording of AEs.

Visit 2 (V2): Baseline Assessments (Day -1): Subjects completed the Baseline assessments (Day -1 [V2]) 1 day prior to study drug administration including: Tellegen Absorption Scale (TAS), NEO-FFI, SCL-90, PANAS, PET, RMET, SVO, TEQ, SSR, SWM, RVP, SSTS, Paired Associates Learning (PAL), vital signs, urine drug screen, review of prior and concomitant medications and recording of AEs. During this visit, subjects joined in a 2 hour group session with the study psychiatrist, lead therapist, chaperones, and all subjects to be dosed the following day. The subject was informed about what to expect during the session. All questions were answered. Subjects who had additional questions or concerns were able to have a 1:1 preparatory session with the assigned chaperone.

Visit 3 (V3): Drug Administration (Day 0): The subject was asked to eat a light breakfast at least two hours prior to coming to the clinic for study drug administration. On Day 0 (V3), the subject underwent the SSTS, had vital signs obtained, medications reviewed, AEs recorded and eligibility reviewed prior to being randomized to study drug. The study drug was administered to up to six subjects simultaneously in individual beds separated by a curtain. The subject was invited to put on eyeshades and headphones, lie down and listen to calming music for the rest of the session (six hours). The subject was supported 1:1 with a chaperone and supervised by the study psychiatrist and lead therapist.

The effects of psilocybin usually started about 20 to 30 min after administration, becoming most intense in the first 90 to 120 min and gradually subsiding in about 5 to 6 hours. The subjects were asked to remain in the room for the duration of the session regardless of the intensity of the effects, preferably 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. A light meal and fruit was available for the subject after the session. After the acute effects of study drug

administration had subsided, all subjects were assessed for safety and asked to complete the following assessments: PANAS and 5D-ASC. Medications used, if any, during study drug administration session, and adverse events were recorded. The subjects also discussed their psilocybin experience with their therapist. The subject was discharged 6 to 8 hours post dose when, in the opinion of the investigator, the acute effects of psilocybin were resolved. After the acute effects of study drug administration subsided, subjects returned home accompanied by a family member, friend, or chaperone. The therapists checked with the subjects by phone at the end of the day to ensure that the subject arrived home safely.

Visit 4 (V4): Safety Assessments (Day 1): Subjects returned to the clinic the next morning (Day 1 [V4]) for safety assessments, including but not limited to: SSTS, vital signs, clinical laboratory tests, review of concomitant medications and AEs and a one-on-one discussion about the subject's experience with the subject's assigned therapist.

Visit 5 (V5): Follow up visit (Day 7 or at Early Termination): Psychometric assessments were completed remotely on Day 7 (V5) or at Early Termination (ET): NEO-FFI, SCL-90, LCI, PET, RMET, SVO, TEQ, SSR, SSTS, SWM, RVP, PAL, review of concomitant medication and recording of AEs. Additionally, at Day 7 (V5) the ERT, IED, OTS, Verbal Fluency and Digit Span Forward tests were conducted.

Visit 6: Follow up visit (Day 28): The SSTS, SWM, RVP, PAL, review of concomitant medication and recording of AEs were obtained at Day 28 (V6).

Visit 7: Follow up Visit (Day 84): The NEO-FFI, SCL-90, LCI, PET, RMET, SVO, TEQ and SSR was obtained remotely at Day 84 (V7). If the subject discontinued the study early, this visit was performed early.

Recording of adverse events and prior/concomitant medication was performed at each visit.

Table 2A summarizes the assessments and procedures that were performed at each visit.

Table 2A: Schedule of Visits

	Screening	Baseline	Treatment Period				
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7 (EOS/ET)**
Day	**-56 to -2**	**-1**	**0**	**1**	**7**	**28**	**84**
Allowed Window					**± 1 Day**	**± 3 Days**	**± 7 Days**
Place of Testing	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Remote[1]**	**Remote[1]**	**Remote[1]**
Assessments and Procedures							
ICF							
Medical and Psychiatric History	X						
MINI	X						
MSIBPD	X						
TAS[2]		X					
NEO-FFI[2]		X			X		X
SCL-90[2]		X			X		X
LCI[2]					X		X
Eligibility Review	X	X	X[3]				
Randomization			X[3]				
Preparatory Session[4]		X	X	X[5]			
Study Drug Administration			X				
PANAS[2]		X	X[6]				
5D-ASC[2]			X[6]				

	Screening	Baseline	Treatment Period				
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7 (EOS/ET)**
Day	**-56 to -2**	**-1**	**0**	**1**	**7**	**28**	**84**
Allowed Window					**± 1 Day**	**± 3 Days**	**± 7 Days**
Place of Testing	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Remote[1]**	**Remote[1]**	**Remote[1]**
Social Cognition Panel[2]							
PET		X			X		X
RMET		X			X		X
SVO		X			X		X
TEQ		X			X		X
SSR		X			X		X
Exploratory Assessments							
ERT[7]					X		
IED[7]					X		
OTS[7]					X		
Verbal Fluency[8]					X		
Digit Span Forward[8]					X		
Safety Assessments							
SSTS[2]	X	X	X[3]	X	X	X	
SWM[9]		X			X	X	
RVP[9]		X			X	X	

	Screening	Baseline	Treatment Period				
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7 (EOS/ET)**
Day	**-56 to -2**	**-1**	**0**	**1**	**7**	**28**	**84**
Allowed Window					**± 1 Day**	**± 3 Days**	**± 7 Days**
Place of Testing	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Remote[1]**	**Remote[1]**	**Remote[1]**
PAL[9]		X			X	X	
Physical Examination	X						
Vital Signs[10]	X	X	X[3]	X			
Body Weight, Height and BMI	X						
12-lead ECG	X						
Clinical Laboratory Tests [11]	X			X			
Urine Drug Screen	X	X					
Urine Pregnancy Test[12]	X	X					
Documentation of Contraceptive Method[13]	X						
Prior/Concomitant Medications[14]	X	X	X	X	X	X	X
AE[15]	X	X	X	X	X	X	X

[1] This session may be done remotely by telephone or in the clinic.

[2] Paper and pencil test.

[3] Obtained prior to study drug administration.

[4] A preparatory session will be conducted in a group session at Baseline (Day -1, V2) and prior to dosing on Day 0 (V3). An individual session will also be conducted at Baseline (Day -1, V2).

[5] A group discussion will be held about the study drug administration experience.

[6] Obtained immediately after study drug administration.

[7] Part of the Cambridge Cognition Panel; to be recorded on the digital platform.

[8] Part of the Cambridge Cognition Panel; to be recorded during the telephone interview.

[9] To be done electronically. V 1, subjects will carry out a practice session of the computerized tests, but the data will not be used.

[10] Vital signs (sitting BP, pulse, oral body temperature and respiratory rate) are to be obtained after the subject has been seated for at least 3 min.

[11] *Chemistry:* albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, bilirubin (direct, indirect and total), calcium, chloride, creatine kinase, creatinine, GGT, glucose, LDH, lipase, magnesium, phosphate, potassium, protein-total, sodium, BUN and uric acid.

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.

[12] All females.

[13] For females of childbearing potential and all males; site is to document method of contraception agreed to be used by each subject.

[14] Prior medications will be obtained until dosing of study drug, thereafter, concomitant medications will be recorded.

[15] All AEs occurring after the subject signs the ICF and up to the last study event will be recorded. Any AEs occurring before the start of treatment (i.e. , before the administration of the study drug on Day 0 [V3]) will be recorded in the medical history.

Results

The phase I, randomized, double-blind, placebo-controlled study to evaluate the effects of 10mg and 25mg COMP360 (psilocybin) compared with placebo in healthy subjects was performed. **Fig. 9A** shows a timeline of the study.

A total of 89 subjects were enrolled in the study. Of these, 30 participants were randomized to receive 25 mg psilocybin, 30 to 10 mg psilocybin, and 29 to placebo. All subjects randomized to both psilocybin arms completed the study; four (13.8%) placebo-treated subjects did not complete all study visits (three were lost to follow-up and one subject discontinued due to a protocol violation). Some subjects that completed the study did not complete certain cognition and/or emotional processing assessments at all timepoints. In these instances, analyses only included the available data and missing data were not imputed. Table 2B shows the number of subjects from each treatment arm that completed the study.

Table 2B: Number of Subjects that Completed the Phase 1 Clinical Study

Parameter	Statistic	Psilocybin (25mg) (N=30)	Psilocybin (10mg) (N=30)	Placebo (N=29)	Overall (N=89)
Number of randomized population	N	30	30	29	89
Number of completions	N (%)	30 (100.0)	30 (100.0)	25 (86.2)	85 (95.5)
Number of early terminations	N (%)	0	0	4 (13.8)	4 (4.5)
Reason for early terminations					
Lost to follow-up	N (%)	0	0	3 (10.3)	3 (3.4)
Protocol violation	N (%)	0	0	1 (3.4)	1 (1.1)

Abbreviation: N=number of subjects.

During administration of psilocybin, each subject received one-on-one support from a trained assisting therapist and each dosing session was supervised by a study psychiatrist and a lead therapist. The study drug was administered simultaneously to up to six participants as a single 5-capsule oral dose (10 mg psilocybin: 2 x 5-mg psilocybin capsules plus 3 x placebo capsules; 25 mg psilocybin: 5 x 5-mg psilocybin capsules; placebo: 5 x placebo capsules). Twenty-five dosing sessions were completed, with up to six participants dosed simultaneously per session. Each session lasted approximately 6 to 8 hours with subjects encouraged to relax and engage in introspection for the duration. After the acute effects of the study drug had subsided, subjects were discharged.

A diagram of the study is presented in **Fig. 9B,** which shows the number of subjects that completed screening (Visit 1), baseline measurements (Visit 2), and drug administration (Visit 3).

The mean (SD) age of the subjects was 36.1 (9.06) years with the range of 20 to 59 years. The majority of the subjects were white (72 [80.9%]). Forty-eight (53.9%) of subjects were male and 41 (46.1%) were female. The mean (SD) BMI of the subjects was 23.2 (3.37) kg/m^2 with the range of 18 to 35 kg/m^2. Thirty- three (37.1%) subjects had prior psilocybin experience. For subjects with prior psilocybin experience, the last experience was at least one year prior to the signing of the informed consent form. The subjects were highly educated with approximately 97% having an education level over Undergraduate/Higher National Diploma. The average age and gender of the subjects was consistent across the treatment arms.

The demographics of the subjects are revealed in Table 2C.

Table 2C: Demographics of Subjects in Healthy Volunteer Study

Parameter	25 mg psilocybin (n= 30)	10 mg psilocybin (n=30)	Placebo (n=29)	Overall (n=89)
Sex, n (%)				
Male	16 (53.3)	16 (53.3)	16 (55.2)	48 (53.9)
Female	14 (46.7)	14 (46.7)	13 (44.8)	41 (46.1)
Ethnicity, n (%)				
White	25 (83.3)	27 (90.0)	20 (69.0)	72 (80.9)
Asian	2 (6.7)	1 (3.3)	3 (10.3)	6 (6.7)
Mixed	2 (6.7)	1 (3.3)	1 (3.4)	4 (4.5)
Black	-	-	1 (3.4)	1 (1.1)
Other	1 (3.3)	1 (3.3)	4 (13.8)	6 (6.7)
Age at screening, years				
Mean (SD)	36.6 (10.29)	36.1 (9.25)	35.6 (7.69)	36.1 (9.06)
BMI, kg/m^2				
Mean (SD)	23.0 (3.74)	23.0 (2.89)	23.7 (3.49)	23.2 (3.37)
Prior psilocybin experience n (%)				
Yes	11 (36.7)	15 (50.0)	7 (24.1)	33 (37.1)
No	19 (63.3)	15 (50.0)	22 (75.9)	56 (62.9)
Educational level n (%)				
A level/NVQ	2 (6.7)	1 (3.3)	0	3 (3.4)

Parameter	25 mg psilocybin (n= 30)	10 mg psilocybin (n=30)	Placebo (n=29)	Overall (n=89)
Undergrad/Higher National Diploma	9 (30.0)	11 (36.7)	10 (34.5)	30 (33.7)
Masters or postgraduate diploma	16 (53.3)	16 (53.3)	15 (51.7)	47 (52.8)
PhD	3 (10.0)	2 (6.7)	4 (13.8)	9 (10.1)

89 subjects were administered psilocybin or placebo in a dosing session, which contained between **1** and **6** subjects. **Fig. 9C** shows the group size of the dosing sessions.

All subjects that were administered psilocybin (groups 1 and 2) completed the study.

511 adverse events (AEs) were reported throughout the 12-week duration of the study: 217 in the 25mg psilocybin arm (reported by 96.7% of subjects); 203 in the 10mg psilocybin arm (reported by 96.7% of subjects); and 91 in the placebo arm (reported by 89.7% of subjects). Of these, 473 (92.6%) AEs were deemed by the investigators to potentially be related to study treatment, including 208 (95.9%) in the 25 mg psilocybin arm, 188 (92.6%) in the 10 mg psilocybin arm, and 77 (84.6%) in the placebo arm. There were no serious adverse events or adverse events that led to withdrawal.

Overall, the most common treatment-emergent adverse events (TEAEs) by system organ class were Psychiatric disorders, Nervous system disorders, General disorders and administration site conditions, Gastrointestinal disorders and Infections and infestations. The most frequent TEAEs were (number of events in parentheses): Illusion (56), Mood altered (54), Hallucination visual (44), Headache (33), Fatigue (21), Somatic hallucination (19), Euphoric mood (14), Paraesthesia (12), Tension headache (12), Time perception altered (11), Hallucination, auditory (9), Affect lability (9), Feeling of relaxation (8), Emotional disorder (8), Hypoaesthesia (7).

Table 2D shows a summary of treatment-emergent adverse events.

Table 2D: Summary of Treatment-Emergent Adverse Events

	Psilocybin 25 mg (N=30)		Psilocybin 10 mg (N=30)		Placebo (N=29)	
	N (%)	Events	N (%)	Events	N (%)	Events
Any TEAE	29 (96.7)	217	29 (96.7)	203	26 (89.7)	91

	Psilocybin 25 mg (N=30)		Psilocybin 10 mg (N=30)		Placebo (N=29)	
	N (%)	Events	N (%)	Events	N (%)	Events
Any serious TEAE	0	0	0	0	0	0
Any TEAE related to study treatment	29 (96.7)	208	29 (96.7)	188	23 (79.3)	77
Any serious TEAE related to study treatment	0	0	0	0	0	0
Any severe TEAE	10 (33.3)	29	10 (33.3)	22	1 (3.4)	2
Any Selected TEAE	27 (90.0)	106	27 (90.0)	106	11 (37.9)	24
Any TEAE leading to study discontinuation	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0

Percentages are based on the number of subjects in each treatment group.

Adverse events are coded using MedDRA.

Abbreviations: N=Number of subjects; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=Treatment-emergent adverse event.

A summary of TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) SOC and PTs is presented in Table 2E and **Fig. 9D.**

Table 2E: Summary of Treatment-Emergent Adverse Events by MedDRA Primary SOC and PT With >10% Subjects in Each Treatment Arm (Safety Population)

System Organ Class Preferred Term	Psilocybin 25mg (N=30)		Psilocybin 10mg (N=30)		Placebo (N=29)	
	N (%)	Events	N (%)	Events	N (%)	Events
Any TEAE	29 (96.7)	217	29 (96.7)	203	26 (89.7)	91
Gastrointestinal disorders	5 (16.7)	5	4 (13.3)	4	5 (17.2)	5

System Organ Class Preferred Term	Psilocybin 25mg (N=30)		Psilocybin 10mg (N=30)		Placebo (N=29)	
	N (%)	Events	N (%)	Events	N (%)	Events
Nausea	3 (10.0)	3	1 (3.3)	1	1 (3.4)	1
General disorders and administration site conditions	15 (50.0)	18	17 (56.7)	27	7 (24.1)	7
Fatigue	8 (26.7)	8	9 (30.0)	10	3 (10.3)	3
Feeling abnormal	0	0	4 (13.3)	4	0	0
Feeling of relaxation	1 (3.3)	1	3 (10.0)	5	2 (6.9)	2
Infections and infestations	4 (13.3)	4	4 (13.3)	4	5 (17.2)	5
Investigations	1 (3.3)	1	2 (6.7)	2	4 (13.8)	5
Musculoskeletal and connective tissue disorders	3 (10.0)	4	1 (3.3)	1	3 (10.3)	3
Nervous system disorders	25 (83.3)	43	21 (70.0)	35	12 (41.4)	16
Headache	15 (50.0)	16	9 (30.0)	12	5 (17.2)	5
Hypoaesthesia	3 (10.0)	4	2 (6.7)	2	1 (3.4)	1
Paraesthesia	4 (13.3)	4	4 (13.3)	4	4 (13.8)	4
Tension headache	6 (20.0)	6	3 (10.0)	3	3 (10.3)	3
Psychiatric disorders	29 (96.7)	135	27 (90.0)	121	16 (55.2)	44
Affect lability	3 (10.0)	3	5 (16.7)	5	1 (3.4)	1
Emotional disorder	5 (16.7)	6	2 (6.7)	2	0	0
Euphoric mood	7 (23.3)	8	7 (23.3)	7	0	0
Hallucination	2 (6.7)	2	3 (10.0)	3	0	0
Hallucination, auditory	4 (13.3)	4	4 (13.3)	4	1 (3.4)	1
Hallucination, tactile	4 (13.3)	4	2 (6.7)	2	0	0
Hallucination, visual	21 (70.0)	22	18 (60.0)	20	2 (6.9)	2
Illusion	18 (60.0)	26	19 (63.3)	25	4 (13.8)	5
Mental fatigue	3 (10.0)	3	0	0	0	0
Mood altered	15 (50.0)	25	13 (43.3)	23	6 (20.7)	9
Somatic hallucination	5 (16.7)	6	8 (26.7)	8	4 (13.8)	5
Time perception altered	6 (20.0)	6	2 (6.7)	2	3 (10.3)	3
Respiratory, thoracic and mediastinal disorders	3 (10.0)	3	0	0	2 (6.9)	2

Percentages are based on the number of subjects in each treatment group.
Adverse events are coded using MedDRA.
Abbreviations: N=Number of subjects; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred term; SOC=System organ class; TEAE=Treatment-emergent adverse event.

The majority of TEAEs were of mild to moderate severity (Table 2F). The incidence of severe TEAEs was higher in the subjects receiving psilocybin (both 10 mg and 25 mg) compared to placebo (29 in the psilocybin 25 mg arm, 22 in the psilocybin 10 mg arm, and two in the placebo arm).

The majority of the severe TEAEs were psychiatric disorders for both the psilocybin 10 mg and 25 mg arms. The incidence of Illusion, Hallucination (visual), Mood altered, Headache,

Fatigue and Euphoric mood were higher in the subjects receiving psilocybin (both 10 and 25mg) compared to placebo.

Table 2F: Summary of TEAES by MedDRA Primary System Organ Class (SOC) and preferred term (PT) with >10% Subjects in Each Treatment Arm by Worst Severity (Safety Population)

System Organ Class Preferred Term	Worst Severity	Psilocybin 25mg (N=30)		Psilocybin 10mg (N=30)		Placebo (N=29)	
		N (%)	Events	N (%)	Events	N (%)	Events
Any TEAE	Mild	3 (10.0)	14	6 (20.0)	12	16 (55.2)	40
	Moderate	16 (53.3)	52	13 (43.3)	38	9 (31.0)	23
	Severe	10 (33.3)	29	10 (33.3)	22	1 (3.4)	2
Gastrointestinal disorders	Mild	4 (13.3)	4	3 (10.0)	3	3 (10.3)	3
	Moderate	1 (3.3)	1	1 (3.3)	1	2 (6.9)	2
	Severe	0	0	0	0	0	0
General disorders and administration site conditions	Mild	8 (26.7)	8	13 (43.3)	17	3 (10.3)	3
	Moderate	6 (20.0)	7	3 (10.0)	6	3 (10.3)	3
	Severe	1 (3.3)	1	1 (3.3)	1	1 (3.4)	1
Fatigue	Mild	3 (10.0)	3	6 (20.0)	6	2 (6.9)	2
	Moderate	5 (16.7)	5	2 (6.7)	3	1 (3.4)	1
	Severe	0	0	1 (3.3)	1	0	0
Feeling abnormal	Mild	0	0	3 (10.0)	3	0	0
	Moderate	0	0	1 (3.3)	1	0	0
	Severe	0	0	0	0	0	0
Infections and infestations	Mild	4 (13.3)	4	2 (6.7)	2	4 (13.8)	4
	Moderate	0	0	2 (6.7)	2	1 (3.4)	1
	Severe	0	0	0	0	0	0
Investigations	Mild	1 (3.3)	1	2 (6.7)	2	3 (10.3)	4
	Moderate	0	0	0	0	1 (3.4)	1
	Severe	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	Mild	2 (6.7)	3	0	0	3 (10.3)	3
	Moderate	1 (3.3)	1	1 (3.3)	1	0	0
	Severe	0	0	0	0	0	0
Nervous system disorders	Mild	16 (53.3)	24	15 (50.0)	23	11 (37.9)	15
	Moderate	8 (26.7)	10	6 (20.0)	8	1 (3.4)	1
	Severe	1 (3.3)	1	0	0	0	0
Headache	Mild	10 (33.3)	10	9 (30.0)	12	4 (13.8)	4
	Moderate	5 (16.7)	5	0	0	1 (3.4)	1
	Severe	0	0	0	0	0	0
Hypoaesthesia	Mild	3 (10.0)	4	2 (6.7)	2	1 (3.4)	1
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Paraesthesia	Mild	3 (10.0)	3	4 (13.3)	4	4 (13.8)	4
	Moderate	1 (3.3)	1	0	0	0	0

System Organ Class Preferred Term	Worst Severity	Psilocybin 25mg (N=30)		Psilocybin 10mg (N=30)		Placebo (N=29)	
		N (%)	Events	N (%)	Events	N (%)	Events
	Severe	0	0	0	0	0	0
Tension headache	Mild	4 (13.3)	4	1 (3.3)	1	3 (10.3)	3
	Moderate	2 (6.7)	2	2 (6.7)	2	0	0
	Severe	0	0	0	0	0	0
Psychiatric disorders	Mild	4 (13.3)	5	4 (13.3)	6	8 (27.6)	13
	Moderate	16 (53.3)	45	13 (43.3)	29	7 (24.1)	15
	Severe	9 (30.0)	27	10 (33.3)	21	1 (3.4)	1
Affect lability	Mild	2 (6.7)	2	3 (10.0)	3	0	0
	Moderate	1 (3.3)	1	2 (6.7)	2	1 (3.4)	1
	Severe	0	0	0	0	0	0
Emotional disorder	Mild	1 (3.3)	1	1 (3.3)	1	0	0
	Moderate	4 (13.3)	5	1 (3.3)	1	0	0
	Severe	0	0	0	0	0	0
Euphoric mood	Mild	3 (10.0)	3	0	0	0	0
	Moderate	4 (13.3)	4	6 (20.0)	6	0	0
	Severe	0	0	1 (3.3)	1	0	0
Hallucination	Mild	0	0	0	0	0	0
	Moderate	2 (6.7)	2	3 (10.0)	3	0	0
	Severe	0	0	0	0	0	0
Hallucination, auditory	Mild	1 (3.3)	1	1 (3.3)	1	0	0
	Moderate	3 (10.0)	3	1 (3.3)	1	1 (3.4)	1
	Severe	0	0	2 (6.7)	2	0	0
Hallucination, visual	Mild	3 (10.0)	3	3 (10.0)	3	1 (3.4)	1
	Moderate	13 (43.3)	13	8 (26.7)	8	1 (3.4)	1
	Severe	5 (16.7)	5	7 (23.3)	7	0	0
Illusion	Mild	3 (10.0)	4	7 (23.3)	7	3 (10.3)	4
	Moderate	10 (33.3)	12	12 (40.0)	16	0	0
	Severe	5 (16.7)	7	0	0	1 (3.4)	1
Mood altered	Mild	2 (6.7)	3	2 (6.7)	2	0	0
	Moderate	6 (20.0)	7	5 (16.7)	8	6 (20.7)	6
	Severe	7 (23.3)	9	6 (20.0)	9	0	0
Somatic hallucination	Mild	2 (6.7)	2	1 (3.3)	1	4 (13.8)	5
	Moderate	2 (6.7)	2	7 (23.3)	7	0	0
	Severe	1 (3.3)	2	0	0	0	0
Time perception altered	Mild	2 (6.7)	2	1 (3.3)	1	3 (10.3)	3
	Moderate	4 (13.3)	4	1 (3.3)	1	0	0
	Severe	0	0	0	0	0	0

Percentages are based on the number of subjects in each treatment group.
Adverse events are coded using MedDRA.
Abbreviations: N=Number of subjects; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred term; SOC=System organ class; TEAE=Treatment-emergent adverse event.

Selected adverse events are displayed in Table 2G. The most frequent of these adverse events were Mood altered (n=57), Illusion (n=56), Hallucination visual (n=44), Somatic hallucination (n=19) and Euphoric mood (n=15).

Table 2G: Summary of selected TEAEs of by MedDRA primary system organ class and preferred term

System Organ Class Preferred Term	Psilocybin 25mg (N=30)		Psilocybin 10mg (N=30)		Placebo (N=29)	
	N (%)	Events	N (%)	Events	N (%)	Events
Selected TEAE	27 (90.0)	106	27 (90.0)	106	11 (37.9)	24
Nervous system disorders	0	0	2 (6.7)	2	0	0
Memory impairment	0	0	1 (3.3)	1	0	0
Psychomotor skills impaired	0	0	1 (3.3)	1	0	0
Psychiatric disorders	27 (90.0)	106	27 (90.0)	104	11 (37.9)	24
Affect lability	3 (10.0)	3	5 (16.7)	5	1 (3.4)	1
Change in sustained attention	0	0	2 (6.7)	2	0	0
Depressed mood	2 (6.7)	2	1 (3.3)	1	1 (3.4)	1
Dissociative identity disorder	2 (6.7)	2	1 (3.3)	2	0	0
Euphoric mood	7 (23.3)	8	7 (23.3)	7	0	0
Hallucination	2 (6.7)	2	3 (10.0)	3	0	0
Hallucination, auditory	4 (13.3)	4	4 (13.3)	4	1 (3.4)	1
Hallucination, gustatory	0	0	1 (3.3)	1	0	0
Hallucination, olfactory	1 (3.3)	1	1 (3.3)	1	0	0
Hallucination, tactile	4 (13.3)	4	2 (6.7)	2	0	0
Hallucination, visual	21 (70.0)	22	18 (60.0)	20	2 (6.9)	2
Somatic hallucination	5 (16.7)	6	8 (26.7)	8	4 (13.8)	5
Illusion[Error! Reference source not found.]	18 (60.0)	26	19 (63.3)	25	4 (13.8)	5
Mood altered	15 (50.0)	25	13 (43.3)	23	6 (20.7)	9
Substance-induced psychotic disorder[b]	1 (3.3)	1	0	0	0	0

Percentages are based on the number of subjects in each treatment group.
Adverse events are coded using MedDRA.
Abbreviations: N=Number of subjects; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred term; SOC=System organ class; TEAE=Treatment-emergent adverse event.

b. This subject became behaviorally disinhibited during the acute drug experience. After a medical assessment, 2.5 mg oromucosal midazolam was administered. The subject recovered with no sequelae and was discharged 11 hours after receiving the study intervention. This event was not considered to be an SAE, and no clinically significant ongoing effects were noted at follow-up.

Mood alteration (MedDRA term is 'mood altered') was one of the most frequently reported adverse events. 57 AEs of mood alteration were reported (grouped according to regulatory requirements in MedDRA terms).

Table 2H shows the frequency of specific 'mood altered' AEs. Most 'mood altered' AEs were positive or neutral in nature (96%).

Table 2H: Reported Mood Altered Events (ranked by incidence in the 25 mg psilocybin group)

Description of 'Mood altered' Event	25 mg psilocybin (n=30	10 mg psilocybin (n=30)	Placebo (n=29)	Overall (n=89)
Introspection	8	5	2	15
Reflections	4	3	2	9
Sense of oneness	2	4	0	6
Increased empathy	2	2	0	4
Contemplative state	1	1	0	2
Laughter	1	1	0	2
Clarity of thought	1	0	0	1
Increased compassion	1	0	0	1
Increased creativity	1	0	0	1
Increased sense of connectedness	1	0	0	1
More socially upbeat	1	0	0	1
Saw themselves from a new perspective	1	0	0	1
Being less judgmental	0	1	0	1
Feeling more moody/sensitive	0	1	0	1
Feeling rested	0	1	0	1
Increased wit	0	1	0	1
Sense of openness	0	1	0	1
Unusual appreciation of music	0	0	1	1
Calm	0	0	1	1
Feeling of adrenaline release	0	0	1	1
Negative mood	0	0	1	1

The median duration of adverse events in all treatment arms across the 12-week trial was one day, as shown in **Fig. 9E.** 67 % of all adverse events appeared and resolved on day 0 (day of dosing). 92 % of adverse events likely to be psychedelic in nature were resolved on the day of onset or within a day of onset

The efficacy of psilocybin was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB variables analysed are shown in Table 2I.

Table 21: CANTAB Variables Analyzed During Phase 1 Study

Test	Domain Tested	Outcome Variable	Variable Code
Primary and secondary efficacy and safety			
PAL, SWM, RVP (Safety)	Global cognition	CANTAB global functioning composite	CANTAB composite (+ve)
PAL	Episodic memory	Total errors adjusted	PALTEA (-ve)
SWM	Working memory	Between errors	SWMBE (-ve)
SWM	Executive function	Strategy	SWMS (-ve)
RVP	Sustained attention	A' prime	RVPA (+ve)
Exploratory efficacy			
ERT	Emotion perception	Percent correct	ERTPC (+ve)
OTS	Planning	Problems solved on first choice	OTSPSFC (+ve)
IED	Cognitive flexibility	Total errors	IEDYERT (-ve)

Abbreviations: CANTAB=Cambridge Neuropsychological Test Automated Battery; ERT=Emotion Recognition Test; ERTPC=Emotion Recognition Test percent correct; IED=Intra-Extra Dimensional Set Shift; IEDYERT=Intra-Extra Dimensional Set Shift total errors; OTS=One Touch Stockings of Cambridge; OTSPSFC=One Touch Stockings of Cambridge problems solved on first choice; PAL=Paired Associates Learning; PALTEA=Paired Associates Learning total errors adjusted; RVP=Rapid Visual Information Processing; RVPA=Rapid Visual Information Processing A' prime; SWM=Spatial Working Memory; SWMBE=Spatial Working Memory between errors; SWMS=Spatial Working Memory strategy.

-ve lower scores indicate better performance

+ve higher scores indicate better performance

The Paired Associates Learning (PAL) test of the CANTAB was used to assess the effect of psilocybin on memory. The result of the PAL was reported as PAL Total Errors Adjusted (PALTEA). A lower score on the PALTEA indicated better performance (lower error count) and a positive change from baseline indicated worse performance (higher error count). On average, there was a numeric improvement in performance for the 10mg and 25mg psilocybin groups from Baseline to Day 28 whereas the placebo group showed a decrease in performance from Baseline to Day 28 as shown in **Fig. 9F.** Both the 10 mg psilocybin and 25 mg psilocybin groups showed on average of about a 2-point improvement in performance compared to the placebo group (LS mean difference from placebo) at Day 28 as shown in **Fig. 9G.**

The Spatial Working Memory (SWM) of CANTAB was also used to assess the effect of psilocybin on memory. The result of the SWM was reported as Spatial Working Memory between

errors (SWMBE). A lower SWMBE score indicated better performance. Therefore, a negative change from baseline indicates better performance (lower error count), and a positive change from baseline indicates worse performance (higher error count). On average, performance improved numerically across psilocybin-treated and placebo treated groups from Baseline to Day 28, with the 25 mg psilocybin group showing a similar performance to that of placebo. The 10 mg group improved less, on average, with a higher error score at Day 28 than placebo as shown in **Fig. 9H.** The least squares (LS) mean difference indicated the 10mg group performed less well on average than the placebo group at both Day 7 and Day 28, whilst the 25mg group performs similarly to the placebo group at Day 28 **(Fig. 9I).** However, for these effects there was insufficient evidence of change.

The spatial working memory strategy score (SWMS) of CANTAB was also assessed. Lower SWMS scores indicated better performance. On average, there was a small numeric improvement in performance from Baseline to Day 28 across 10mg and 25mg psilocybin groups and placebo **(Fig. 9J).** The least squares mean difference indicated that the 25mg psilocybin group and 10mg psilocybin group performed similar to placebo at Day 7. However, the 25 mg group performed on average slightly better than the placebo, whilst the 10 mg group performed on average slightly worse than placebo at Day 28 **(Fig. 9K).**

The rapid visual information processing test of CANTAB, RVP A Prime (RPVA) was also assessed. Higher scores on the RVPA indicated better performance. As shown in **Fig. 9L,** there was an average numeric improvement in performance across all groups. The ANOVA suggested there was no evidence of an overall change in RVPA as a result of exposure to intervention. For both the 10mg group and 25mg group, the LS mean difference from placebo at Day 28 was different from placebo **(Fig. 9M).** This suggested a separation in performance at Day 28 between the psilocybin dose groups and the placebo group.

No main effect for psilocybin status or interaction (psilocybin status by visit by dose) was observed for the CANTAB composite measure in the subjects who completed the assessments without a major protocol deviation as part of the analysis of covariance (ANCOVA) analysis (p-values > 0.05), suggesting no consistent differential performance due to previous exposure to psilocybin.

Least square means estimates indicated an improvement from Baseline to Day 7 and Day 28 in those psilocybin-naive subjects in the placebo group. Conversely, least square means estimates indicated improvement from Baseline to Day 28 for those from the 10 mg psilocybin dose group who were previously exposed to psilocybin only. This improvement from baseline to Day 28 in the psilocybin experienced subjects was also an improvement relative to placebo. **Fig.**

9V shows the CANTAB composite score for psilocybin-naive subjects (0) and psilocybin-experienced subjects (1).

However, for the 25mg group, an improvement to Day 28 was observed irrespective of previous psilocybin exposure. This improvement was also higher relative to placebo.

The Emotional Recognition Task (ERT) test of the CANTAB was used to assess the effect of psilocybin. The result of the ERT was reported as the ERT percent correct (ERTPC). Higher ERTPC scores indicated better performance. No evidence of a difference was observed between the 25mg and 10mg psilocybin groups and placebo nor between the 25mg and 10mg psilocybin groups at Day 7 (Fig. 9N).

The One Touch Stockings of CANTAB was used to assess the effect of psilocybin on executive function. A higher OTS Problems Solved on First Choice indicated better performance. There was insufficient evidence of a difference observed between the 25mg and 10mg psilocybin groups or difference of these groups from placebo for performance on OTSPSFC at Day 7 (Fig. 90).

The Intra-Extra Dimensional Set Shift of CANTAB was used to assess the effect of psilocybin on executive function. A lower IED Total Errors (IEDYERT) score indicated better performance. No difference in performance on IEDYERT was observed between psilocybin-treated groups or between placebo and psilocybin-treated groups at Day 7 (Fig. 9P).

The composite score of the CANTAB was assessed. The composite score was derived from Z scores for each CANTAB outcomes measure (PALTEA, SWMBE, SWMS, RVPA). A higher global composite score indicated a better performance. Both psilocybin-treated groups and placebo showed an improvement in performance over time from Baseline to Day 28 (Fig. 9Q).

The LS mean difference from placebo was different from 0 for the 10 mg group at Day 7 (Fig. 9R, LS mean difference = -0.18320, p value ~ 0.04460, effect size 0.53;). For the 10mg group, performance increased again at Day 28 suggesting no adverse effects of the 10mg dose compared with placebo.

The verbal fluency test was completed at Visit 5 via phone. This task was reliant on the integrity of a range of cognitive abilities including executive functions such as planning and working memory. Subjects were asked to name different category exemplars (e.g. animals) in one minute. No statistically significant difference in the verbal fluency score was observed compared to placebo for both the psilocybin 10 mg (p-value 0.7635) and 25 mg arm (p-value 0.8412) (Fig. 9S).

The digit span forward test was completed at Visit 5 via phone. This task was a measure of number storage capacity, a common measure of short-term memory. No statistically significant

difference in digit span scores was observed compared to placebo for both the psilocybin 10mg (p value 0.6432) and 25 mg arm (p value 0.1 147) **(Fig. 9T).**

The Five-Dimensional Altered States of Consciousness (5D-ASC) Questionnaire was administered, as summarized in Table 2J. **Fig. 9U** summarizes the results of the Five Dimensional - Altered States of Consciousness (5D-ASC).

Table 2J: Analysis of variance (ANOVA) Model F-Tests for the 5D-ASC

Parameter	Source	DF	SS	MS	F-value	Pvalue
Oceanic boundlessness	Treatment	2	47562.11748	23781.05874	62.66	<0.0001
	FPE	1	406.80610	406.80610	1.07	0.3035
Dread of ego dissolution	Treatment	2	13243.54504	6621.77252	21.81	<0.0001
	FPE	1	398.65320	398.65320	1.31	0.2552
Visual restructuralisation	Treatment	2	55584.85537	27792.42768	113.68	<0.0001
	FPE	1	31.46543	31.46543	0.13	0.7207
Auditory alteration	Treatment	2	11807.54615	5903.77308	26.51	<0.0001
	FPE	1	171.64561	171.64561	0.77	0.3825
Vigilance reduction	Treatment	2	12983.11807	6491.55904	14.43	<0.0001
	FPE	1	1669.03601	1669.03601	3.71	0.0576
Experience of unity	Treatment	2	45746.16992	22873.08496	38.52	<0.0001
	FPE	1	419.21831	419.21831	0.71	0.4033
Spiritual experience	Treatment	2	44295.01759	22147.50880	33.47	<0.0001
	FPE	1	106.12236	106.12236	0.16	0.6899
Blissful state	Treatment	2	48144.44507	24072.22254	39.91	<0.0001
	FPE	1	21.22999	21.22999	0.04	0.8517
Insightfulness	Treatment	2	51518.58287	25759.29144	45.01	<0.0001
	FPE	1	82.51431	82.51431	0.14	0.7051
Disembodiment	Treatment	2	38024.97280	19012.48640	39.19	<0.0001
	FPE	1	432.56944	432.56944	0.89	0.3478
Impaired control and cognition	Treatment	2	14847.05053	7423.52526	18.90	<0.0001
	FPE	1	367.97317	367.97317	0.94	0.3359
Anxiety	Treatment	2	13654.18304	6827.09152	19.43	<0.0001
	FPE	1	90.95683	90.95683	0.26	0.6122
Complex imagery	Treatment	2	55098.80129	27549.40064	103.59	<0.0001
	FPE	1	148.07986	148.07986	0.56	0.4577
Elementary imagery	Treatment	2	72036.48627	36018.24314	61.13	<0.0001
	FPE	1	411.61569	411.61569	0.70	0.4057
Audio-visual synaesthesia	Treatment	2	79483.55646	39741.77823	79.53	<0.0001
	FPE	1	421.45066	421.45066	0.84	0.3611
Changed meaning of percepts	Treatment	2	34476.31342	17238.15671	24.58	<0.0001
	FPE	1	319.13449	319.13449	0.46	0.5018

Note: F-test from ANOVA model with fixed effect for treatment and FPE.
Abbreviations: 5D-ASC=Five-Dimensional Altered States of Consciousness questionnaire; ANOVA=Analysis of variance; DF=Degrees of freedom; FPE=Former psilocybin experience; MS=Mean sum of squares; SS=Sum of squares; TAS=Tellegen absorption scale.

There were differences detected among treatment groups for each domain of the 5D-ASC. Prior exposure to psilocybin had no apparent effect on this scale. Differences between the placebo and psilocybin groups in each of the primary domains of the 5D-ASC scale were observed. The Dread of Ego Dissolution and Auditory Alteration subscales also showed a difference between psilocybin doses (10mg and 25mg; $p \leq 0.05$), with the 25mg psilocybin group showing higher scores than the 10mg psilocybin group on both domains, as shown in Table 2K.

Table 2K: Differences between placebo and psilocybin-treated groups in the primary dimensions of the 5D-ASC

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin 25mg - 10mg
Oceanic boundlessness							
Post-Treatment Day 0	n	30	30	29	-	-	-
	Mean	62.9	55.7	8.0	54.9	47.7	7.2
	95% CI	-	-	-	44.48, 65.32	37.11, 58.26	-2.86, 17.29
	pvalue	-	-	-	<0.0001	<0.0001	0.1581
Dread of ego dissolution							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	31.9	21.7	1.2	30.6	20.5	10.1
	95% CI	-	-	-	21.32, 39.95	11.03, 29.95	1.13, 19.16
	pvalue	-	-	-	<0.0001	<0.0001	0.0278
Visual restructuralisation							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	65.2	59.1	6.5	58.7	52.6	6.1
	95% CI	-	-	-	50.35, 67.07	44.11, 61.09	-1.98, 14.20
	pvalue	-	-	-	<0.0001	<0.0001	0.1366
Auditory alteration							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	30.7	20.3	1.7	29.1	18.6	10.5
	95% CI	-	-	-	21.07, 37.03	10.46, 26.66	2.77, 18.21
	pvalue	-	-	-	<0.0001	<0.0001	0.0083
Vigilance reduction							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	45.7	35.3	15.3	30.4	20.0	10.3
	95% CI	-	-	-	19.03, 41.72	8.51, 31.55	-0.62, 21.31
	pvalue	-	-	-	<0.0001	0.0009	0.0642

Note: LS means and p-values from ANOVA model with fixed effects for treatment and FPE.
Abbreviations: 5D-ASC=Five-Dimensional Altered States of Consciousness questionnaire; ANOVA=Analysis of variance; CI=Confidence interval; FPE=Former psilocybin experience; LS=Least squares; N=All subjects randomized; n=Subjects with post-treatment assessments.

As shown in Table 2L below, differences between each of the psilocybin dose groups and placebo were observed for the 11 sub-scores of the 5D-ASC ($p \leq 0.0001$). There was insufficient evidence for differences between the psilocybin doses except for the anxiety and complex imagery subscales which showed a higher mean value in the psilocybin 25 mg dose group compared to psilocybin 10mg ($p \leq 0.001$).

Table 2L: Differences between placebo and psilocybin-treated groups in the 11 sub¬dimensions of the 5D-ASC

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin 25mg - 10mg
Experience of unity							
Post-Treatment Day 0	N	30	30	26	-	-	-
	Mean	60.9	54.4	7.2	53.6	47.1	6.5
	95% CI	-	-	-	40.60, 66.66	33.89, 60.35	-6.09, 19.11
	p-value	-	-	-	<0.0001	<0.0001	0.3070
Spiritual experience							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	57.9	48.7	4.2	53.7	44.6	9.2
	95% CI	-	-	-	39.98, 67.50	30.61, 58.55	-4.14, 22.46
	p-value	-	-	-	<0.0001	<0.0001	0.1745
Blissful state							
Post-Treatment Day 0	n	29	30	26	-	-	-
	Mean	61.9	59.1	8.2	53.6	50.9	2.8
	95% CI	-	-	-	40.39, 66.90	37.54, 64.22	-10.03, 15.56
	p-value	-	-	-	<0.0001	<0.0001	0.6683
Insightfulness							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	64.4	53.9	6.3	58.2	47.6	10.5
	95% CI	-	-	-	45.38, 70.97	34.64, 60.62	-1.83, 22.92
	p-value	-	-	-	<0.0001	<0.0001	0.0937
Disembodiment							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	53.8	52.7	6.9	46.9	45.8	1.1
	95% CI	-	-	-	35.08, 58.64	33.81, 57.73	-10.30, 12.48
	p-value	-	-	-	<0.0001	<0.0001	0.8490
Impaired control and cognition							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	32.7	27.9	1.8	30.9	26.2	4.7
	95% CI	-	-	-	20.33, 41.53	15.42, 36.94	-5.50, 15.00
	p-value	-	-	-	<0.0001	<0.0001	0.3593

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin 25mg - 10mg
Anxiety							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	32.4	15.7	1.1	31.3	14.6	16.7
	95% CI	-	-	-	21.25, 41.30	4.39, 24.75	7.01, 26.39
	p-value	-	-	-	<0.0001	0.0056	0.0010
Complex imagery							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	64.9	53.0	4.4	60.5	48.6	11.9
	95% CI	-	-	-	51.76, 69.20	39.70, 57.41	3.49, 20.36
	p-value	-	-	-	<0.0001	<0.0001	0.0061
Elementary imagery							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	76.9	76.5	13.0	64.0	63.6	0.4
	95% CI	-	-	-	51.00, 76.97	50.40, 76.76	-12.15, 12.96
	p-value	-	-	-	<0.0001	<0.0001	0.9489
Audio-visual synaesthesia							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	75.4	74.7	8.1	67.3	66.6	0.7
	95% CI	-	-	-	55.38, 79.29	54.51, 78.79	-10.87, 12.24
	p-value	-	-	-	<0.0001	<0.0001	0.9064
Changed meaning of percepts							
Post-Treatment Day 0	n	30	30	26	-	-	-
	Mean	46.1	46.6	2.2	43.9	44.4	-0.5
	95% CI	-	-	-	29.73, 58.05	30.00, 58.76	-14.19, 13.20
	p-value	-	-	-	<0.0001	<0.0001	0.9430

Note: LS means and p-values from ANOVA model with fixed effects for treatment and FPE.
Abbreviations: 5D-ASC=Five-Dimensional Altered States of Consciousness questionnaire; ANOVA=Analysis of variance; CI=confidence interval; FPE=Former psilocybin experience; LS=least squares; N=AII subjects randomized; n=Subjects with post-treatment assessments.

The Positive and Negative Affects Schedule (PANAS) score was also evaluated to measure the effect of psilocybin. For the change in PANAS score (from pre- to post-treatment), an effect of treatment was observed for positive affect ($p = 0.02$) but not for negative affect ($p = 0.0604$). The ANCOVA model components are shown in Table 2M.

Table 2M: F-tests from Analysis of Covariance Model: PANAS

Parameter	Source	DF	SS	MS	F-value	P-value
PANAS – Negative	Treatment	2	54.3731933	27.1865967	2.90	0.0604
	FPE	1	0.0197343	0.0197343	0.00	0.9635
	Baseline score	1	298.2929518	298.2929518	31.86	<0.0001
PANAS – Positive	Treatment	2	507.1469094	253.5734547	4.10	0.0200
	FPE	1	174.4461646	174.4461646	2.82	0.0968
	Baseline score	1	710.6961764	710.6961764	11.49	0.0011
Source: Emotional Processing Table 14.8.1.12 Abbreviations: ANCOVA=Analysis of covariance; DF=Degrees of freedom; MS=Mean sum of squares; PANAS=Positive and Negative Affect Schedule; SS=Sum of squares.						

Prior psilocybin experience did not have a significant impact on the change in PANAS score, but the baseline value was highly predictive, with higher pre-treatment scores predicting a greater increase after dosing.

As shown in Table 2N below, the placebo group showed a reduction in positive affect from baseline to the day of dosing which was not observed in the psilocybin groups ($p < 0.03$). By contrast, the 25mg psilocybin group had a mean increase in negative affect of 1.3, compared to a slight decrease observed in the 10mg group ($p = 0.0218$) and the placebo group ($p = 0.0989$).

Table 2N: Summary of PANAS - Change from Baseline After Treatment on Day 0

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin 25mg - 10mg
PANAS – Negative							
Post-treatment Day 0	n	29	30	29	-	-	-
	Mean	1.3	-0.6	-0.1	1.4	-0.5	1.9
	95% CI	-	-	-	-0.26, 2.99	-2.16, 1.09	0.28, 3.51
	p value	-	-	-	0.0989	0.5164	0.0218
PANAS – Positive							
Post-treatment Day 0	n	29	30	29	-	-	-
	Mean	-0.4	0.7	-5.0	4.6	5.7	-1.0
	95% CI	-	-	-	0.48, 8.79	1.49, 9.87	-5.14, 3.05
	pvalue	-	-	-	0.0293	0.0085	0.6126

Note: LS means and p-values from ANCOVA model with fixed effects for treatment and FPE, and baseline score as covariate.
Abbreviations: ANCOVA=Analysis of covariance; CI=confidence interval; FPE=Former psilocybin experience; LS=least squares; N=All subjects randomized; n=Subjects with post-treatment assessments; PANAS=Positive and Negative Affect Schedule.

The Pictorial Empathy Test (PET), Reading the Mind in the Eyes Test (RMET), Scale of Social Responsibility (SSR), Social Value Orientation (SVO), and Toronto Empathy Questionnaire (TEQ) were performed. Table 20 summarizes the results of the mixed model for repeated measures (MMRM) analysis for each of the aforementioned social cognition panel scales measured on Day 7 and Day 84 after study drug administration.

Table 20: F-Tests from MMRM Model: PET, RMET, SSR, SVO, and TEQ

Parameter	Source	DF	Denominator DF	F-value	Pvalue
PET	Baseline score	1	82.753690	0.33	0.5690
	FPE	1	82.739811	1.64	0.2035
	Treatment	2	81.827569	2.66	0.0761
	Visit	1	80.165106	3.16	0.0794
	Treatment x Visit	2	80.123570	0.01	0.9889
RMET	Baseline score	1	79.642446	13.11	0.0005
	FPE	1	81.293995	0.30	0.5841
	Treatment	2	81.089435	0.09	0.9109
	Visit	1	78.718169	0.58	0.4502
	Treatment x Visit	2	78.697428	0.11	0.8983
SSR global	Baseline score	1	78.029198	1.76	0.1890
	FPE	1	77.981354	2.57	0.1130
	Treatment	2	77.535686	1.73	0.1846
	Visit	1	74.336261	0.69	0.4076
	Treatment x Visit	2	74.149063	0.17	0.8465
SSR fulfilling expectation	Baseline score	1	79.708607	7.43	0.0079
	FPE	1	80.530339	1.10	0.2965
	Treatment	2	79.898753	1.17	0.3164
	Visit	1	77.391208	0.16	0.6881
	Treatment x Visit	2	77.356175	1.82	0.1682
SSR compliance social rules	Baseline score	1	81.040786	15.30	0.0002
	FPE	1	79.293376	0.10	0.7527
	Treatment	2	78.731740	1.44	0.2440
	Visit	1	75.158892	0.00	0.9739
	Treatment x Visit	2	74.971352	0.02	0.9843
SVO angle	Baseline score	1	84.293719	2.33	0.1305
	FPE	1	81.152189	0.02	0.8978
	Treatment	2	80.655666	2.81	0.0661
	Visit	1	80.233253	3.68	0.0588
	Treatment x Visit	2	80.245032	0.02	0.9821
SVO type	Baseline score	1	83.474000	14.15	0.0003
	FPE	1	80.219127	0.05	0.8176
	Treatment	2	79.202003	0.99	0.3770
	Visit	1	78.469668	1.19	0.2783
	Treatment x Visit	2	78.517417	0.00	0.9975
TEQ	Baseline score	1	78.310229	10.05	0.0022
	FPE	1	80.793937	0.07	0.7882
	Treatment	2	79.633057	0.83	0.4381
	Visit	1	77.965918	0.08	0.7725

Parameter	Source	DF	Denominator DF	F-value	Pvalue
	Treatment x Visit	2	77.943131	0.13	0.8800

Note: F-tests from a MMRM analysis with change from baseline score as the dependent variable. Model has fixed effects for treatment, visit, FPE, and treatment by visit interaction, visit as the repeating factor, subject as a random effect, and baseline score as a covariate. Abbreviations: DF=Degrees of freedom; FPE=Former psilocybin experience; MMRM=Mixed model for repeated measures; PET=Pictorial Empathy Test; RMET=Reading the Eyes in the Mind Test; SSR=Scale of Social Responsibility; SVO=Social Value Orientation; TEQ=Tellegen Absorption Questionnaire.

No differences among treatment groups for change from baseline values of RMET, SSR, SVO Type, orTEQ were found ($p > 0.05$ in all cases). P-values were approaching the < 0.05 level for PET and SVO Angle. In each statistical model, the baseline score was typically the best independent predictor of change, with higher pre-treatment scores predicting a greater increase after dosing.

Table 2P shows tests of pairwise differences between treatment groups in the MMRM model for each of the parameters at Day 7 and Day 84.

Table 2P: Summary of PET, RMET, SSR, SVO, and TEQ Results - Change from Baseline on Day 7 and Day 84

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin 25mg - 10mg
PET							
Day 7	n	29	30	26	-	-	-
	Mean	0.0	-0.3	-0.1	0.2	-0.1	0.3
	95% CI	-	-	-	0.11, 0.42	-0.39, 0.15	0.02, 0.54
	p-value	-	-	-	0.2429	0.3659	0.0360
Day 84	n	27	30	23			
	Mean	-0.1	-0.3	-0.2	0.1	-0.1	0.3
	95% CI	-	-	-	-0.12, 0.41	-0.39, 0.15	0.00, 0.52
	p-value	-	-	-	0.2851	0.3807	0.0464
RMET							
Day 7	n	29	30	26	-	-	-
	Mean	0.4	0.4	0.3	0.2	0.1	0.0
	95% CI	-	-	-	-1.44, 1.74	-1.43, 1.69	-1.50, 1.55
	p-value	-	-	-	0.8505	0.8719	0.9748
Day 84	n	27	30	23	-	-	-
	Mean	0.4	0.1	-0.1	0.5	0.2	0.3

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin 25mg - 10mg
	95% CI	-	-	-	-1.29, 2.28	-1.53, 1.95	-1.39, 1.97
	p-value	-	-	-	0.5806	0.8103	0.7339
SSR global							
Day 7	n	26	29	25	-	-	-
	Mean	-0.3	-2.0	-3.2	2.8	1.2	1.6
	95% CI	-	-	-	0.50, 6.18	-2.16, 4.56	-1.58, 4.86
	p-value	-	-	-	0.0941	0.4783	0.3141
Day 84	n	26	28	20	-	-	-
	Mean	0.1	-1.8	-2.1	2.2	0.3	1.8
	95% CI	-	-	-	-0.94, 5.29	-2.83, 3.49	-1.04, 4.71
	p-value	-	-	-	0.1687	0.8338	0.2068
SSR fulfilling expectations							
Day 7	n	28	29	26	-	-	-
	Mean	-0.0	-0.1	-0.2	0.2	0.1	0.1
	95% CI	-	-	-	-0.04, 0.35	-0.14, 0.26	-0.10, 0.28
	p-value	-	-	-	0.1233	0.5468	0.3461
Day 84	n	26	29	22	-	-	-
	Mean	-0.0	-0.2	-0.1	0.0	-0.1	0.2
	95% CI	-	-	-	0.16, 0.23	-0.32, 0.08	-0.04, 0.34
	p-value	-	-	-	0.7238	0.2461	0.1114
SSR compliance social rules							
Day 7	n	27	30	25	-	-	-
	Mean	0.0	-0.1	-0.1	0.1	0.0	0.1
	95% CI	-	-	-	-0.07, 0.34	-0.19, 0.22	-0.08, 0.32
	p-value	-	-	-	0.1983	0.8831	0.2331
Day 84	n	26	29	20	-	-	-
	Mean	0.0	-0.1	-0.1	0.1	-0.0	0.1
	95% CI	-	-	-	-0.08, 0.35	-0.22, 0.22	-0.06, 0.33
	p-value	-	-	-	0.2242	0.9949	0.1827
SVO angle							
Day 7	n	29	30	26	-	-	-

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin 25mg - 10mg
	Mean	0.5	1.8	-1.6	2.1	3.4	-1.3
	95% CI	-	-	-	-1.32, 5.58	-0.05, 6.85	-4.60, 2.04
	p-value	-	-	-	0.2233	0.0531	0.4466
Day 84	n	27	30	23	-	-	-
	Mean	-0.9	0.1	-3.3	2.4	3.4	-1.0
	95% CI	-	-	-	-1.16, 6.06	-0.16, 6.97	-4.34, 2.44
	p-value	-	-	-	0.1803	0.0613	0.5785
SVO type							
Day 7	n	29	30	26	-	-	-
	Mean	0.1	0.1	-0.0	0.1	0.1	-0.0
	95% CI	-	-	-	-0.11, 0.24	-0.07, 0.28	-0.21, 0.13
	p-value	-	-	-	0.4551	0.2460	0.6630
Day 84	n	27	30	23	-	-	-
	Mean	0.0	0.1	-0.0	0.1	0.1	-0.0
	95% CI	-	-	-	-0.10, 0.24	-0.06, 0.28	-0.20, 0.12
	p-value	-	-	-	0.4321	0.1993	0.5994
TEQ							
Day 7	n	29	30	26	-	-	-
	Mean	0.0	-0.1	-0.1	0.2	0.1	0.1
	95% CI	-	-	-	-0.08, 0.38	-0.16, 0.31	-0.14, 0.30
	p-value	-	-	-	0.2004	0.5425	0.4846
Day 84	n	26	30	23	-	-	-
	Mean	-0.0	-0.1	-0.2	0.1	0.1	0.0
	95% CI	-	-	-	0.13, 0.36	-0.15, 0.34	-0.21, 0.25
	p-value	-	-	-	0.3420	0.4403	0.8454

Note: LS means and p-values from a MMRM analysis with change from baseline score as the dependent variable. Model has fixed effects for treatment, visit, FPE, and treatment by visit interaction, visit as the repeating factor, subject as a random effect, and baseline score as a covariate.

Abbreviations: CI=Confidence interval; FPE=Former psilocybin experience; LS=Least squares; MMRM=Mixed model for repeated measures; N=All subjects randomized; n=Subjects with post-treatment assessments; PET=Pictorial Empathy Test; RMET=Reading the Eyes in the Mind Test; SSR=Scale of Social Responsibility; SVO=Social Value Orientation; TEQ=Tellegen Absorption Questionnaire.

There was no difference between either psilocybin group and placebo on PET, RMET, SSR, SVO, or TEQ at either timepoint. The reduction in PET score was greater with 10mg than 25mg psilocybin at both Day 7 and Day 84, but no differences were detected between psilocybin groups and placebo (for all $p > 0.05$).

The Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI) and Symptom Checklist-90 Item (SCL-90) were administered. Details of the MMRM applied to the change from baseline scores for the NEO-FFI and SCL-90 are provided below in Table 2Q.

Table 2Q: F-Tests from MMRM Model: NEO-FFI and SCL-90

Parameter	Source	DF	Denominator DF	F-value	P-value
NEO-neuroticism	Baseline score	1	76.979208	5.74	0.0190
	FPE	1	77.840113	0.93	0.3383
	Treatment	2	77.617527	0.25	0.7790
	Visit	1	73.682482	7.74	0.0068
	Treatment x Visit	2	73.686883	0.68	0.5082
NEO-extraversion	Baseline score	1	78.374755	14.95	0.0002
	FPE	1	78.343718	0.96	0.3292
	Treatment	2	78.626820	0.02	0.9845
	Visit	1	73.855914	4.63	0.0348
	Treatment x Visit	2	73.862965	0.81	0.4477
NEO-openness	Baseline score	1	74.806595	6.32	0.0141
	FPE	1	77.275373	0.00	0.9549
	Treatment	2	76.498330	1.41	0.2503
	Visit	1	74.250319	0.24	0.6261
	Treatment x Visit	2	74.270107	0.61	0.5446
NEO agreeableness	Baseline score	1	78.147167	5.13	0.0263
	FPE	1	78.408944	0.40	0.5292
	Treatment	2	78.501462	0.37	0.6886
	Visit	1	73.826719	5.46	0.0221
	Treatment x Visit	2	73.845054	0.29	0.7497
NEO conscientiousness	Baseline score	1	77.124423	4.82	0.0312
	FPE	1	77.786049	1.86	0.1764
	Treatment	2	76.183832	1.12	0.3301
	Visit	1	74.486641	4.14	0.0454
	Treatment x Visit	2	74.477293	0.56	0.5741
SCL-90 - somatisation	Baseline score	1	79.868863	0.55	0.4613
	FPE	1	80.705565	1.49	0.2256
	Treatment	2	81.464446	0.34	0.7150
	Visit	1	78.071807	0.94	0.3357

Parameter	Source	DF	Denominator DF	F-value	P-value
	Treatment x Visit	2	78.070370	0.42	0.6559
SCL-90 obsessive compulsive	Baseline score	1	80.547228	14.11	0.0003
	FPE	1	82.484967	3.28	0.0736
	Treatment	2	81.559194	0.59	0.5556
	Visit	1	80.073966	0.33	0.5691
	Treatment x Visit	2	80.064909	0.42	0.6554
SCL-90 interpersonal sensitivity	Baseline score	1	80.121543	3.70	0.0580
	FPE	1	80.874433	3.13	0.0807
	Treatment	2	82.579702	0.30	0.7403
	Visit	1	77.993603	1.43	0.2350
	Treatment x Visit	2	77.991778	0.28	0.7566
SCL-90 depression	Baseline score	1	80.197894	2.91	0.0918
	FPE	1	80.342361	1.84	0.1784
	Treatment	2	81.303470	0.07	0.9345
	Visit	1	77.391519	0.31	0.5802
	Treatment x Visit	2	77.389587	0.06	0.9420
SCL-90 anxiety	Baseline score	1	80.428114	12.64	0.0006
	FPE	1	81.212552	0.15	0.7015
	Treatment	2	82.662941	0.18	0.8352
	Visit	1	78.366882	0.13	0.7161
	Treatment x Visit	2	78.359701	0.13	0.8758
SCL-90 anger hostility	Baseline score	1	79.979660	54.73	<0.0001
	FPE	1	79.997333	0.83	0.3636
	Treatment	2	76.243037	0.22	0.8001
	Visit	1	76.998093	3.73	0.0571
	Treatment x Visit	2	76.998109	0.66	0.5194
SCL-90 phobic anxiety	Baseline score	1	80.002443	72.72	<0.0001
	FPE	1	80.012526	1.66	0.2014
	Treatment	2	83.392134	0.25	0.7801
	Visit	1	77.011834	0.35	0.5541
	Treatment x Visit	2	77.011930	0.11	0.9001
SCL-90 paranoid ideation	Baseline score	1	82.462798	2.09	0.1525
	FPE	1	81.511417	3.38	0.0695
	Treatment	2	80.282457	1.35	0.2658
	Visit	1	79.911612	1.70	0.1954
	Treatment x Visit	2	79.848142	0.59	0.5550
SCL-90 psychoticism	Baseline score	1	79.993358	0.75	0.3887
	FPE	1	81.786131	0.93	0.3379
	Treatment	2	81.672000	0.18	0.8367
	Visit	1	79.185707	0.18	0.6729

Parameter	Source	DF	Denominator DF	F-value	P-value
	Treatment x Visit	2	79.178467	0.67	0.5153

Note: F-tests from a MMRM analysis with change from baseline score as the dependent variable. Model has fixed effects for treatment, visit, FPE, and treatment by visit interaction, visit as the repeating factor, subject as a random effect, and baseline score as a covariate. Abbreviations: DF=Degrees of freedom; FPE=Former psilocybin experience; MMRM=Mixed model for repeated measures; NEO-FFI= Neuroticism Extraversion Openness - Five Factor Inventory; SCL-90=Symptom Checklist - 90 Item.

The strongest predictor of change in each scale was the baseline value itself, which was positively correlated with the change after dosing, whereas prior exposure to psilocybin had no detectable effect.

Table 2R presents the LS means and pairwise treatment comparisons based on the change from baseline scores for NEO-FFI and SCL-90.

Table 2R: Summary of NEO-FFI and SCL-90 Results - Change from Baseline on Day 7 and Day 84

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
NEO neuroticism							
Day 7	n	28	28	26	-	-	-
	Mean	0.2	0.2	0.4	0.2	-0.2	-0.0
	95% CI	-	-	-	-2.31, 1.96	-2.28, 1.93	-2.04, 2.04
	p value	-	-	-	0.8714	0.8701	0.9997
Day 84	n	26	27	22	-	-	-
	Mean	0.8	2.1	1.8	-1.0	0.3	-1.3
	95% CI	-	-	-	-3.56, 1.60	-2.24, 2.83	-3.70, 1.14
	pvalue	-	-	-	0.4512	0.8152	0.2957
NEO extraversion							
Day 7	n	28	28	26	-	-	-
	Mean	0.3	0.3	-0.1	0.5	0.4	0.1
	95% CI	-	-	-	-1.19, 2.10	-1.28, 2.06	-1.56, 1.68
	pvalue	-	-	-	0.5848	0.6411	0.9399
Day 84	n	26	27	22	-	-	-
	Mean	-0.7	-0.9	-0.2	-0.5	-0.7	0.2
	95% CI	-	-	-	-2.52, 1.55	-2.70, 1.39	-1.78, 2.13
	pvalue	-	-	-	0.6383	0.5255	0.8617
NEO openness							
Day 7	n	28	28	26	-	-	-
	Mean	0.4	0.3	-0.8	1.2	1.1	0.1
	95% CI	-	-	-	-0.25, 2.71	-0.37, 2.59	-1.34, 1.58
	pvalue	-	-	-	0.1030	0.1405	0.8717
Day 84	n	26	27	22	-	-	-
	Mean	0.3	0.4	-0.7	0.4	1.1	-0.7

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
	95% CI	-	-	-	-1.28, 2.14	-0.60, 2.79	-2.31, 0.97
	pvalue	-	-	-	0.6190	0.2026	0.4202
NEO agreeableness							
Day 7	n	28	30	26	-	-	-
	Mean	0.1	-0.2	0.2	-0.1	-0.4	0.4
	95% CI	-	-	-	-1.50, 1.31	-1.89, 0.99	-1.04, 1.75
	pvalue	-	-	-	0.8963	0.5355	0.6115
Day 84	n	26	27	22	-	-	-
	Mean	-0.9	-0.9	-0.2	-0.7	-0.8	0.1
	95% CI	-	-	-	-2.37, 1.03	-2.47, 0.97	-1.56, 1.72
	pvalue	-	-	-	0.4339	0.3873	0.9242
NEO conscientiousness							
Day 7	n	28	28	26	-	-	-
	Mean	0.1	-0.1	-0.6	0.7	0.4	0.3
	95% CI	-	-	-	-0.91, 2.34	-1.20, 2.10	-1.34, 1.86
	pvalue	-	-	-	0.3855	0.5892	0.7446
Day 84	n	26	27	22	-	-	-
	Mean	-0.1	-1.3	-1.5	1.4	0.2	1.2
	95% CI	-	-	-	-0.40, 3.20	-1.56, 2.05	-0.56, 2.88
	pvalue	-	-	-	0.1243	0.7873	0.1844
SCL-90 – somatisation							
Day 7	n	29	30	26	-	-	-
	Mean	0.1	0.1	-0.0	0.1	0.1	-0.0
	95% CI	-	-	-	-0.06, 0.17	-0.06, 0.18	-0.12, 0.11
	pvalue	-	-	-	0.3299	0.3277	0.9794
Day 84	n	27	30	23	-	-	-
	Mean	0.0	0.0	0.0	0.0	0.0	0.0
	95% CI	-	-	-	-0.10, 0.18	-0.13, 0.15	-0.11, 0.16
	pvalue	-	-	-	0.6109	0.9229	0.6672
SCL-90 obsessive compulsive							
Day 7	n	29	30	26	-	-	-
	Mean	-0.1	-0.1	-0.2	0.1	0.1	-0.0
	95% CI	-	-	-	-0.09, 0.28	-0.09, 0.29	-0.18, 0.18
	pvalue	-	-	-	0.3052	0.3049	0.9908
Day 84	n	27	30	23	-	-	-
	Mean	-0.1	-0.0	-0.1	0.0	0.1	-0.1
	95% CI	-	-	-	-0.17, 0.21	-0.11, 0.28	-0.25, 0.12
	pvalue	-	-	-	0.8118	0.3756	0.4944
SCL-90 interpersonal sensitivity							
Day 7	n	29	30	26	-	-	-
	Mean	0.0	-0.0	0.0	0.0	-0.0	0.1
	95% CI	-	-	-	-0.11, 0.15	-0.17, 0.09	-0.07, 0.18
	pvalue	-	-	-	0.8110	0.5479	0.3802
Day 84	n	27	30	23	-	-	-
	Mean	0.0	0.0	0.1	-0.0	-0.1	0.0
	95% CI	-	-	-	-0.21, 0.13	-0.23, 0.11	-0.14, 0.18

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
	pvalue	-	-	-	0.6592	0.4992	0.8067
SCL-90 depression							
Day 7	n	29	30	26	-	-	-
	Mean	0.0	0.0	0.0	0.0	0.0	-0.0
	95% CI	-	-	-	-0.17, 0.21	-0.17, 0.22	-0.19, 0.18
	pvalue	-	-	-	0.8566	0.7878	0.9259
Day 84	n	27	30	23	-	-	-
	Mean	0.1	0.1	0.0	0.0	0.0	0.0
	95% CI	-	-	-	0.18, 0.28	-0.19, 0.27	-0.21, 0.23
	pvalue	-	-	-	0.6964	0.7395	0.9501
SCL-90 anxiety							
Day 7	n	29	30	26	-	-	-
	Mean	-0.0	-0.0	-0.0	0.0	-0.0	0.0
	95% CI	-	-	-	-0.12, 0.11	-0.14, 0.10	-0.10, 0.13
	pvalue	-	-	-	0.9312	0.7178	0.7739
Day 84	n	27	30	23	-	-	-
	Mean	-0.0	-0.0	0.0	-0.0	-0.1	0.0
	95% CI	-	-	-	-0.23, 0.13	-0.23, 0.13	-0.17, 0.17
	pvalue	-	-	-	0.5904	0.5588	0.9674
SCL-90 anger hostility							
Day 7	n	29	30	26	-	-	-
	Mean	-0.0	-0.0	0.0	-0.0	-0.0	0.0
	95% CI	-	-	-	-0.09, 0.07	-0.13, 0.03	-0.04, 0.11
	pvalue	-	-	-	0.7591	0.2564	0.3847
Day 84	n	27	30	23	-	-	-
	Mean	0.0	0.0	0.0	-0.0	-0.0	-0.0
	95% CI	-	-	-	-0.16, 0.09	-0.14, 0.11	-0.14, 0.10
	p value	-	-	-	0.5890	0.8112	0.7495
SCL-90 phobic anxiety							
Day 7	n	29	30	26	-	-	-
	Mean	0.0	-0.0	0.0	0.0	-0.0	0.0
	95% CI	-	-	-	-0.03, 0.04	-0.05, 0.03	-0.02, 0.05
	pvalue	-	-	-	0.7815	0.5556	0.3647
Day 84	n	27	30	23	-	-	-
	Mean	0.0	0.0	0.0	0.0	-0.0	0.0
	95% CI	-	-	-	0.04, 0.07	-0.06, 0.05	-0.04, 0.06
	pvalue	-	-	-	0.7081	0.9499	0.6450
SCL-90 paranoid ideation							
Day 7	n	29	30	26	-	-	-
	Mean	0.1	-0.0	-0.0	0.1	0.0	0.1
	95% CI	-	-	-	-0.02, 0.23	-0.09, 0.17	-0.06, 0.19
	p-value	-	-	-	0.1016	0.5489	0.2800
Day 84	n	27	30	23	-	-	-
	Mean	0.1	0.1	-0.0	0.1	0.1	0.0
	95% CI	-	-	-	-0.05, 0.18	-0.05, 0.18	-0.11, 0.11
	p-value	-	-	-	0.2543	0.2863	0.9363

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
SCL-90 psychoticism							
Day 7	n	29	30	26	-	-	-
	Mean	0.0	0.0	0.0	0.0	0.0	0.0
	95% CI	-	-	-	-0.07, 0.08	-0.07, 0.07	-0.06, 0.08
	p-value	-	-	-	0.8196	0.9812	0.8302
Day 84	n	27	30	23	-	-	-
	Mean	0.0	-0.0	0.0	-0.0	-0.0	0.0
	95% CI	-	-	-	-0.08, 0.07	-0.11, 0.04	-0.05, 0.10
	p-value	-	-	-	0.8823	0.3851	0.4476

Note: LS means and p-values from a MMRM with fixed effects for treatment, visit, FPE, and treatment by visit interaction term, with visit as the repeating factor, subject as a random effect, and baseline score as a covariate.
Abbreviations: CI=Confidence interval; DF=Degrees of freedom; FPE=Former psilocybin experience; LS=Least squares; MMRM=Mixed model for repeated measures; N=All subjects randomized; n=Subjects with post-treatment assessments; NEO-FFI= Neuroticism Extraversion Openness - Five Factor Inventory; SCL-90=Symptom Checklist - 90 Item.

Table 2S summarizes the results of the MMRM model applied to LCI parameters measured on Day 7 and Day 84 after study drug administration.

Table 2S: F-Tests from MMRM Model: LCI Measures

Parameter	Source	DF	Denominator DF	F-value	P-value
LCI – absolute change	FPE	1	82.799713	0.04	0.8352
	Treatment	2	82.605786	12.69	<0.0001
	Visit	1	78.162909	0.31	0.5765
	Treatment x Visit	2	78.054268	0.40	0.6740
LCI appreciation for life	FPE	1	82.909504	0.33	0.5661
	Treatment	2	82.198916	12.35	<0.0001
	Visit	1	79.332039	0.02	0.8767
	Treatment x Visit	2	79.170548	0.17	0.8464
LCI self-acceptance	FPE	1	83.843514	0.03	0.8521
	Treatment	2	83.332333	23.73	<0.0001
	Visit	1	81.020342	0.66	0.4199
	Treatment x Visit	2	80.834117	0.98	0.3791
LCI concern for others	FPE	1	83.730773	0.01	0.9302
	Treatment	2	82.680005	7.95	0.0007
	Visit	1	80.322544	0.33	0.5660
	Treatment x Visit	2	80.155567	0.42	0.6578
LCI concern for worldly achievement	FPE	1	82.629869	1.17	0.2826
	Treatment	2	83.456184	3.78	0.0269
	Visit	1	77.542669	0.67	0.4161
	Treatment x Visit	2	77.464305	0.75	0.4750
LCI concern social	FPE	1	82.874879	0.63	0.4297
	Treatment	2	83.174991	2.06	0.1334
	Visit	1	78.231885	1.02	0.3167

Parameter	Source	DF	Denominator DF	F-value	P-value
	Treatment x Visit	2	78.123691	0.21	0.8137
LCI quest for meaning	FPE	1	81.846606	0.04	0.8448
	Treatment	2	82.365281	6.71	0.0020
	Visit	1	76.551800	0.36	0.5495
	Treatment x Visit	2	76.488228	0.11	0.8952
LCI spirituality	FPE	1	83.145868	0.09	0.7617
	Treatment	2	82.820446	5.08	0.0083
	Visit	1	79.406353	0.03	0.8635
	Treatment x Visit	2	79.252439	0.44	0.6459
LCI religiousness	FPE	1	83.221381	0.00	0.9560
	Treatment	2	81.343523	0.71	0.4966
	Visit	1	79.127237	0.01	0.9113
	Treatment x Visit	2	78.990086	0.01	0.9922
LCI appreciation of death	FPE	1	83.009544	0.24	0.6288
	Treatment	2	83.554368	2.48	0.0897
	Visit	1	78.314013	3.04	0.0853
	Treatment x Visit	2	78.209655	0.54	0.5853

Source: Emotional Processing Table 14.8.2.8
Note: F-tests from a MMRM with outcome score as the dependent variable. The model has fixed effects for treatment, visit, FPE, and treatment by visit interaction, visit as the repeating factor, and subject as a random effect.
Abbreviations: DF=Degrees of freedom; FPE=Former psilocybin experience; MMRM=Mixed model for repeated measures; LCI=Line Changes Inventory.

An overall effect of treatment was found for all LCI domains except Concern Social, Religiousness, and Appreciation of Death. No treatment by visit interaction was found in any case, indicating that the treatment effect was consistent over time. Time and prior psilocybin use had no apparent impact on this scale.

LS means and pairwise treatment comparisons for each domain of the LCI scale are summarized in Table 2T below.

Table 2T: Summary of LCI Results on Day 7 and Day 84

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
LCI – absolute change							
Day 7	n	29	30	26	-	-	-
	Mean	0.4	0.5	0.1	0.3	0.4	-0.1
	95% CI	-	-	-	0.14, 0.48	0.20, 0.55	-0.23, 0.11
	pvalue	-	-	-	0.0007	<0.0001	0.4723

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
Day 84	n	27	30	21	-	-	-
	Mean	0.5	0.5	0.1	0.4	0.4	-0.0
	95% CI	-	-	-	0.19, 0.55	0.21, 0.56	-0.19, 0.15
	pvalue	-	-	-	<0.0001	<0.0001	0.8393
LCI appreciation for life							
Day 7	n	29	30	26	-	-	-
	Mean	0.6	0.8	0.2	0.5	0.6	-0.2
	95% CI	-	-	-	0.16, 0.74	0.31, 0.90	-0.44, 0.13
	pvalue	-	-	-	0.0028	<0.0001	0.2762
Day 84	N	27	30	21	-	-	-
	Mean	0.7	0.8	0.2	0.5	0.6	-0.1
	95% CI	-	-	-	0.24, 0.79	0.35, 0.90	-0.37, 0.15
	pvalue	-	-	-	0.0003	<0.0001	0.4037
LCI self-acceptance							
Day 7	N	29	30	26	-	-	-
	Mean	0.6	0.8	0.1	0.5	0.7	-0.1
	95% CI	-	-	-	0.32, 0.75	0.45, 0.88	-0.35, 0.07
	pvalue	-	-	-	<0.0001	<0.0001	0.1938
Day 84	N	27	30	21	-	-	-
	Mean	0.6	0.6	0.1	0.5	0.5	0.0
	95% CI	-	-	-	0.28, 0.76	0.26, 0.75	-0.21, 0.24
	pvalue	-	-	-	<0.0001	<0.0001	0.8961
LCI concern for others							
Day 7	n	29	30	26	-	-	-
	Mean	0.6	0.5	0.1	0.4	0.4	0.0
	95% CI	-	-	-	0.15, 0.71	0.11, 0.67	-0.23, 0.31
	pvalue	-	-	-	0.0034	0.0075	0.7864
Day 84	n	27	30	21	-	-	-
	Mean	0.7	0.5	0.1	0.5	0.4	0.1
	95% CI	-	-	-	0.25, 0.77	0.12, 0.64	-0.12, 0.37
	pvalue	-	-	-	0.0002	0.0046	0.3046

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
LCI concern for worldly achievement							
Day 7	n	29	30	26	-	-	-
	Mean	-0.2	-0.2	-0.0	-0.1	-0.2	0.1
	95% CI	-	-	-	-0.31, 0.02	-0.37, -0.03	-0.11, 0.22
	pvalue	-	-	-	0.0908	0.0197	0.4818
Day 84	n	27	30	21	-	-	-
	Mean	-0.1	-0.2	0.0	-0.1	-0.2	0.1
	95% CI	-	-	-	-0.29, 0.09	-0.44, -0.06	-0.03, 0.33
	pvalue	-	-	-	0.3069	0.0118	0.1050
LCI concern social							
Day 7	n	29	30	26	-	-	-
	Mean	0.2	0.2	0.1	0.2	0.1	0.1
	95% CI	-	-	-	0.01, 0.33	-0.05, 0.27	-0.10, 0.22
	pvalue	-	-	-	0.0412	0.1915	0.4428
Day 84	n	27	30	21	-	-	-
	Mean	0.2	0.2	0.1	0.1	0.1	0.0
	95% CI	-	-	-	-0.06, 0.32	-0.07, 0.32	-0.17, 0.19
	pvalue	-	-	-	0.1741	0.1952	0.9365
LCI quest for meaning							
Day 7	n	29	30	26			
	Mean	0.5	0.5	0.1	0.4	0.4	0.0
	95% CI	-	-	-	0.16, 0.64	0.15, 0.64	-0.23, 0.24
	pvalue	-	-	-	0.0015	0.0018	0.9737
Day 84	n	27	30	21			
	Mean	0.5	0.5	0.1	0.4	0.4	-0.0
	95% CI	-	-	-	0.07, 0.63	0.11, 0.66	-0.30, 0.23
	pvalue	-	-	-	0.0139	0.0070	0.7956
LCI spirituality							
Day 7	n	29	30	26	-	-	-
	Mean	0.4	0.5	0.2	0.2	0.3	-0.1
	95% CI	-	-	-	-0.03, 0.51	0.05, 0.59	-0.34, 0.18

Parameter		Psilocybin 25mg (N=30)	Psilocybin 10mg (N=30)	Placebo (N=29)	Psilocybin 25mg - Placebo	Psilocybin 10mg - Placebo	Psilocybin (25mg - 10mg)
	pvalue	-	-	-	0.0789	0.0204	0.5318
Day 84	n	27	30	21	-	-	-
	Mean	0.5	0.5	0.1	0.4	0.4	-0.0
	95% CI	-	-	-	0.09, 0.65	0.12, 0.68	-0.29, 0.23
	pvalue	-	-	-	0.0105	0.0052	0.7985
LCI religiousness							
Day 7	n	29	30	26	-	-	-
	Mean	0.0	-0.0	0.0	0.0	-0.1	0.1
	95% CI	-	-	-	-0.09, 0.15	-0.17, 0.07	-0.04, 0.19
	pvalue	-	-	-	0.6789	0.4061	0.1991
Day 84	n	27	30	21	-	-	-
	Mean	0.0	-0.0	-0.0	0.0	-0.0	0.1
	95% CI	-	-	-	-0.19, 0.24	-0.25, 0.17	-0.13, 0.26
	pvalue	-	-	-	0.8056	0.7212	0.5143
LCI appreciation of death							
Day 7	n	29	30	26	-	-	-
	Mean	0.1	0.2	0.0	0.1	0.1	-0.0
	95% CI	-	-	-	-0.06, 0.25	-0.03, 0.28	-0.17, 0.13
	pvalue	-	-	-	0.2163	0.1265	0.7511
Day 84	n	27	30	21	-	-	-
	Mean	0.3	0.2	0.1	0.2	0.2	0.0
	95% CI	-	-	-	-0.01, 0.45	-0.05, 0.40	-0.17, 0.25
	pvalue	-	-	-	0.0597	0.1190	0.7010

Note: LS means and p-values from the MMRM with outcome score as the dependent variable. The model has fixed effects for treatment, visit, FPE, and treatment by visit interaction, visit as the repeating factor, and subject as a random effect. Abbreviations: CI=Confidence interval; FPE=Former psilocybin experience; LCI=Line Changes Inventory; LS=least squares; MMRM=Mixed model for repeated measures; N=All subjects randomized; n=Subjects with post-treatment assessments.

Each psilocybin dose group showed a higher absolute change in LCI compared to the placebo group at both Day 7 and Day 84 after drug administration ($p < 0.05$). The effect of each psilocybin dose compared to placebo was < 0.05 for nearly all LCI domains at both timepoints,

notably Appreciation for Life, Self-Acceptance, Concern for Others, and Quest for Meaning. Positive trends were also observed for Spirituality, Concern for Worldly Achievement, and Concern Social. However, Religiousness and Appreciation of Death appeared to be unaffected.

The differences between psilocybin dose effects (10mg versus 25mg) were not statistically significant for any LCI domain at either timepoint.

Psilocybin had an effect on each of the five primary dimensions of the 5D-ASC scale compared to placebo assessed immediately post-treatment ($p \leq 0.0001$). Differences between doses were observed ($p \leq 0.05$) in two cases (Dread of Ego Dissolution and Auditory Alteration), with the 25mg psilocybin group showing higher scores than the 10mg psilocybin group on each of these domains. The 11 sub-scores of the 5D-ASC scale also showed differences between each of the psilocybin dose groups and placebo ($p \leq 0.0001$). Only two of the subscales showed a dose relationship: the mean scores for Anxiety and Complex Imagery were higher in the 25mg dose group than in the 10mg dose group.

At both the 25mg and 10mg doses, subjects treated with psilocybin showed an increase in the LCI absolute change ($p \leq 0.0007$) and in LCI domain scores measuring Appreciation for Life ($p \leq 0.0028$), Self-Acceptance ($p < 0.0001$), Concern for Others ($P \leq 0.0075$), and Quest for Meaning ($p < 0.0139$). These effects were evident regardless of the psilocybin dose administered.

PANAS scores, measured immediately post-treatment, showed a reduction in Positive Affect for placebo-treated subjects, which was not observed in the psilocybin groups ($p < 0.03$). PANAS Negative Affect was increased in the 25mg psilocybin group, compared to a slight decrease in the 10mg group ($p = 0.0218$) and the placebo group ($p = 0.0989$).

There were no consistent or noteworthy trends to suggest that either dose of psilocybin had a short- or long-term effect on PET, RMET, SSR, SVO, or TEQ. Likewise, psilocybin had no detectable effect on changes in NEO-FFI or SCL 90 scales at either Day 7 or Day 84.

There was no evidence of improvement or deterioration in performance on CANTAB tasks as a result of the psilocybin exposure over this 28-day study in this study population of healthy volunteers (inclusion criteria ranging from 20 to 59 years of age). No pro-cognitive effect was detected at Day 7 on the exploratory efficacy outcomes.

On the CANTAB Global Composite score, performance was worse than placebo for the 10 mg psilocybin group at Day 7 ($p < 0.05$). However, this result is due in part to the larger improvement in performance from Baseline by the placebo group at Day 7. For the 10 mg group, performance increases again at Day 28 to a level similar to placebo suggesting no adverse effects of the 10 mg dose compared with placebo. The CANTAB cognitive performance results support the safety and tolerability of the administration of a single 10mg or 25mg dose of psilocybin.

There was no Visit-Dose effect observed on any of the cognitive outcome measures; PALTEA (episodic memory), SWMBE (working memory), SWMS (executive function and planning), RVPA (sustained attention) and Global Cognitive Composite, suggesting there was no consistent and differential performance changes between the placebo and the 10mg and 25mg psilocybin dose groups.

Despite no overall main effect of dose group on RVPA performance (cognitive domain of sustained attention), there was a LS mean difference from placebo for both the 10mg and 25mg groups at Day 28 ($p < 0.05$), suggesting better performance of subjects in the psilocybin dose groups relative to placebo at Day 28.

PANAS scores, measured immediately post-treatment, showed a reduction in Positive Affect for placebo-treated subjects, which was not observed in the psilocybin groups ($p < 0.03$). PANAS Negative Affect was increased in the 25mg psilocybin group, compared to a slight decrease in the 10mg group ($p = 0.0218$) and the placebo group ($p = 0.0989$).

No significant difference in performance was observed between 10mg psilocybin, 25mg psilocybin and placebo groups at Day 7 for the exploratory efficacy outcome measures ERTPC (Emotion recognition), OTSPSFC (executive function, planning and working memory) or IEDYERT (rule acquisition and reversal, flexibility of attention).

Example 4. Clinical Study Examining Psilocybin for the Treatment of Major Depressive Disorder

Aim of study

The aim of this study is to compare the mechanisms, tolerability and efficacy of two high doses of psilocybin versus a 6 week course of a leading antidepressant medication, escitalopram, in major depressive disorder (MDD).

Overview of Study

The main purpose of this design is to test the hypothesis that two doses of psilocybin will show superior efficacy, as well as a different mechanism of action, to the antidepressant medication escitalopram. Previous clinical studies with psilocybin and escitalopram have directed the design of this trial.

This will be a two-arm, active comparator, double-blind, randomized controlled, between-subjects, design in up to 50 completing patients meeting DSM-IV criteria for major depression of a moderate to severe degree. The 50 patients will be randomly allocated to two groups of 25: the experimental condition (condition 1) or the control condition (condition 2). Subjects assigned to the experimental condition will be administered two high doses psilocybin (25 mg, perorally) 3

weeks apart. The first dose of psilocybin will be followed by 6 weeks of daily placebo capsule ingestion (Fig. 10A, condition 1). Subjects assigned to the control condition will receive two presumed inactive doses of psilocybin (1 mg, perorally) 3 weeks apart. The first dose of psilocybin will be followed by 6 weeks of daily escitalopram capsule ingestion (Fig. 10A, condition 2). For both conditions, the first (initial) and second psilocybin dosing sessions will be administered on-site followed by 6 weeks (from initial dosing session) of daily capsule ingestion at home.

The primary endpoint for assessing efficacy is 6 weeks after the initial dosing session. We will use functional magnetic resonance imaging (fMRI) at baseline and six weeks after the initial dosing session to identify how brain activity changes before and after two doses of 25mg psilocybin versus 6 weeks of daily escitalopram. The blind will be broken at the final study visit (6 weeks) after which normal treatment ensues. Un-blinded follow-up will occur for a further 6 months to assess safety and any potential enduring effects.

The main risks of this study are standard risks associated with an acute high dose of psilocybin (e.g. potential acute anxiety and the need for psychological support and supervision during the experience), standard side-effects associated with escitalopram (e.g. drowsiness, dizziness, sleep problems and potential for withdrawal symptoms upon cessation), and standard concerns regarding placebo treatment in depression. Establishing a good connection with referring clinicians, and following standard procedures for psilocybin research, will help to manage and mitigate risk.

Overall, this clinical study will significantly advance our knowledge of the safety, efficacy and mechanism of action of psilocybin for MDD by comparing it with a major conventional treatment for depression. This comparison may lead to the development of psilocybin as an alternative treatment option for patients with MDD.

Study Design

Randomization :

Subjects will be randomly allocated to one of the two conditions using a random sequence generator, which can be found online at: random.org/sequences. The sequence can be initiated and managed by the dispensing pharmacist and a schedule license holder (e.g., Invicro). Blinding and labelling will be done in collaboration with the manufacturing pharmacy (e.g., Guy's and St Thomas', Juniper or Fisher Pharmaceuticals).

Dosing procedure:

Psilocybirr.

Subjects in the experimental group will receive two doses of psilocybin (25 mg, perorally) 3 weeks apart (Fig. 10A, condition 1). This dose has been previously shown to be effective and well tolerated with no serious or unexpected adverse events.

Subjects in the control group will receive two low doses of psilocybin (1 mg, perorally) 3 weeks apart (Fig. 10A, condition 2). This dose has been shown to be a pharmacologically "inert" dose and yet capable of serving as an effective placebo by producing effects via expectancy alone to a similar degree as a non-active placebo.

The merit of using psilocybin in both the experimental and the control group is that the study staff and subjects can be briefed to expect psilocybin in all conditions. Subjects and therapy staff will be encouraged to expect and prepare for up to 25 mg of psilocybin; thus, standardizing preparation and expectations prior to the dosing session.

Escitalopram:

Control subjects will receive the antidepressant escitalopram for 6 weeks (Fig. 10A, condition 2). Escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) and an FDA-approved treatment for major depressive disorder.

Subjects in the control group will receive one 10 mg capsule of escitalopram per day for 3 weeks after their first treatment with inert psilocybin (1 mg). After their second psilocybin (1 mg) dosing session, subjects will be administered 20 mg escitalopram daily (two 10 mg capsules per day) for another 3 weeks (Fig. 10A, condition 2). The 20 mg dose of escitalopram is the recommended maximum dose for the treatment of depression.

The daily dose of escitalopram can be lowered to 10 mg if the 20 mg dose is not well-tolerated. Under these circumstances, subjects would be instructed to take 1 capsule of escitalopram instead of 2 capsules daily.

Subjects in the experimental group will receive a daily placebo instead of escitalopram over the same 6 week period following the initial dosing session (Fig. 10A, condition 1).

Visits:

The study timeline includes 7 visits over a period of 6 weeks to assess the effects of psilocybin and escitalopram on MDD. Fig. 10B provides a summary of the study timeline.

Visit 1: Screening

The initial screening visit includes a number of physical and psychological assessments to determine whether a subject can participate in the clinical trial. The general screening procedure is provided in Table 3A below.

Table 3A. Screening Procedure

No.	Examination Type
1	Informed Consent
2	Full-history and physical examination
3	Psychiatric assessment (MINI)
4	Routine blood screen and sample
5	ECG
6	Urine drug screen
7	Urine pregnancy test
8	Height and weight measurements
9	Breathalyser
10	Clinician-administered rating scales (HAM-D)
11	Secondary outcome measurements

The subject will also partake in an MRI scanner acclimatisation in order to determine whether the subject can tolerate the environment and conditions of the MRI scanner.

Subjects will be psychologically prepared for what to expect at the initial dosing session (Visit 3). The research team will advise the subject to surrender to the experience of the drug. Relaxing music will be used to facilitate a calm, accepting mind-set in the subject. Subjects will be cautioned to expect some anxiety, and they will be encouraged to inform research personnel if they experience anxiety during the dosing session. Consistent with published guidelines on managing psychedelicdrug sessions, subjects will be advised to accept feelings of anxiety and to allow the experience to unfold naturally, without psychological resistance.

Eligible subjects must discontinue use of any anti-depressant medication in a gradual, tapered fashion. Serotonergic antidepressants are known to attenuate the acute psychological effects of psychedelics. Medication withdrawal is typically done via gradual titration (e.g., halving of dose in first week) and the study psychiatrist will oversee this process in correspondence with the patient's general practitioner and/or psychiatrist.

The subject will be randomly allocated to either the experimental condition or the control condition (Fig. 10A). Subjects will be asked to complete the weekly QIDS-16 until 6 weeks after the initial dosing session when the blind is broken. QIDS-16 will enable assessment of the subject's mental health for the duration of the study, facilitating patient monitoring and safety, while providing potentially useful data on weekly mood cycling before and after treatment.

Blood will be collected from the subjects at baseline for the following blood tests shown in Table 3B below.

Table 3B. Baseline Blood Measurements

Blood test	Measurement
Full blood count	Haemoglobin, total white cell count, lymphocytes, neutrophils, platelets
Biochemistry	Sodium, potassium, adjusted calcium, phosphate, albumin and total protein
Renal panel	Creatinine, urea, estimated GFR
Liver panel	Total bilirubin, alanine transaminase, GGT
Pancreas panel	Amylase

Any clinically significant abnormality in the tests listed in Table 3B will result in exclusion from the study. In particular, subjects with any form of renal or hepatic impairment will be excluded.

Subjects will also be encouraged to provide a sample for genetic analysis. Whole blood for genetic analysis will be collected in 2 x 8.5 mL 'PAXgene' tubes and frozen and stored at -80°C for up to 5 years. This time period may be subject to renewal depending on the progress of the study.

Visit 2: Scan 1 and Psychological Preparation

Subjects will undergo an MRI scan lasting no longer than 90 minutes. The scanning session will be followed by psychological preparation with the therapy team (two individuals) who will sit with the subject during their dosing session. Psychological preparation will take approximately 3 hours with two breaks. This visit will take approximately 5.5 hours total.

Visit 3: Dosing Session 1

The first dosing session will take place the day after visit 2 and will take approximately 8 hours to complete. Fig. 10C provides a summary of the schedule for the initial dosing session. The subject will arrive around 9 am and will have been strongly advised to refrain from alcohol for a minimum of 24 hours prior to their arrival as alcohol may compound the effects of psilocybin and potentially interfere with its effects. The subject will undergo initial preparation, including relaxation techniques. At 10:30 am, the subject will receive either 25 mg or 1 mg of psilocybin. The effects of 25 mg psilocybin are typically experienced for 5-6 hours, i.e. subsiding to a low-negligible level at 3:30-4:30 pm. Depending on the magnitude of residual drug effects, subjects will be asked to complete questionnaires starting around 3:30 pm and then participate in a filmed and audio recorded structured interview at between around 4:30-5 pm.

The dosing session will take place in a purpose-built clinical research facility with extensive nursing and emergency support (e.g. Invicro). Efforts will be made to arrange the intervention

room to promote relaxation without compromising medical safety. Mobile phones will be switched off during every session and efforts will be made to minimize unexpected interruptions.

All sessions will be supervised by at least two individuals. A study medical doctor will administer the active psilocybin (25 mg, condition 1) or inert psilocybin (1 mg, condition 2) and be available on site during the dosing sessions. If required, the medical doctor can attend the therapy room within less than 5 minutes.

Research personnel will not initiate conversation with the subject. However, research personnel will respond to the subject if they initiate contact. It is advised that active intervention is kept to a minimum during the acute experience. The subject is encouraged to explore their own mental space. Simple guided imagery may be used to assist relaxation. Breathing techniques may also be used to assist in relaxation.

After approximately 5 hours post-dose, most of the acute subjective effects of psilocybin will have subsided and the subject will undergo a thorough debriefing. This will involve encouraging the subject to give a detailed descriptive account of the experience. Dosing sessions will be video and/or audio recorded. Post-session interviews will also be video and audio recorded for qualitative analyses.

At the end of the dosing day, subjects will be given a course of capsules to be taken daily for the following 6 weeks. Each subject will take one capsule each day for the first 3 weeks and two for the remaining 3 weeks, regardless of whether they are in the experimental condition or the control condition (Fig. 10A). Randomisation will determine whether the capsules are either escitalopram or placebo. Subjects will be asked to take their first capsule as close to 8:00 am as possible the morning after the first dosing session. Subjects are to document exactly when the capsule was taken to ensure standardisation of peak plasma concentration in the escitalopram condition. The peak plasma concentration of escitalopram is reached 3-4 hours post-ingestion.

Visit 4: The day after the first dosing session

One day after the first dosing session (Visit 3), subjects will return to the center to undergo evaluation. The subject will be asked to complete a series of questionnaires, which includes a daily version of QIDS. Subjects will also participate in a structured interview/integration session that asks about their experiences in the initial dosing session and experiences thereafter (e.g., how they slept and how they feel). This visit will take approximately 2-3 hours in total.

Interim period: One week post-treatment

Subject will undergo remote assessment with the study psychiatrist via phone or Skype/Zoom. QIDS measurements will also be conducted weekly throughout the trial. Assessments will be cued via email and/or text using the Psychedelic Survey platform and

completed electronically on Survey Gizmo. The Psychedelic Survey platform is external software that is used to automate reminder emails to a large number of participants over the course of the study. These emails linked participants to questionnaires contained within the separate Survey Gizmo platform (Evans et al., *Frontiers in Human Neuroscience,* 2016; 10), where the data is stored.

Visit 5: The second dosing session

The second dosing session will take place exactly as described in Visit 3 and Fig. 10C above.

Interim period: 4, 5, and 6 weeks following the first dosing session

Remote assessments will be performed as described above. Subjects are free to communicate via email with the study team at any point if issues arise. If additional support is needed, each subject will be allowed a maximum of two additional Skype/Zoom sessions with the study team. This limit is in place in order to avoid an imbalance in the amount of support subjects receive during the study.

Visit 6: The day after the second dosing session

This visit will follow the same structure as described in Visit 4 (the day after the first dosing session).

Visit 7: 6 weeks following the first dosing session

The final study visit will take place 6 weeks after the first dosing session. Subjects will arrive at 10 am and receive a final MRI scan starting at 11 am. The scanning session will last for no longer than 90 minutes. After the scan, subjects will be asked to complete a series of questionnaires. Subjects will also take part in a structured interview in which they will be asked how they currently feel and their feelings over the past 6 weeks. The HAM-D and MADRS assessments will be performed during the interview, which are described in Table 3B below. A comprehensive side-effects questionnaire will also be completed, which asks about side-effects over a 6-week period. A second ECG scan will also be conducted to ensure that there was no effect of psilocybin or escitalopram on heart physiology. A repeat routine blood test as shown in Table 3B will also be conducted. This visit will take approximately 5 hours in total.

At the end of the visit, we will break the blind and inform the subject whether they were in the experimental or control condition. Breaking the blind at this time point will enable us to assess treatment safety and efficacy for both conditions and provide the patient with information on the treatment they received, which may influence future decisions regarding treatment, e.g., whether or not they want to continue with escitalopram if they were in the control group.

If we become concerned about a subject's mental state and associated risks at any point after the final formal visit, we will liaise with the general practitioner and/or mental health practitioners, who may then decide to implement appropriate interventions if necessary.

Assessments at 1-6 months post-treatment:

QIDS-16 will be performed monthly for 6 months following treatment. More comprehensive assessments will also be performed 1, 3, and 6 months after the initial dosing session. Assessments will be cued by telephone and email, completed electronically, and emailed back to the study team. A member of the study team will speak with the subject via telephone or skype at these time points.

6 month post-treatment session:

Remote assessments will be performed as described above. A structured interview will also be carried out and recorded, either via Skype, telephone, or in person if the subject prefers.

The data collected from this study will be used to gather new information about the effects of psilocybin versus the standard anti-depressant medication escitalopram for the treatment of MDD. Data will be tabulated and descriptive parameters derived. The study is powered for a baseline versus week 6 t-test on the QIDS-16 (condition 1 vs condition 2) and this is the primary efficacy outcome and endpoint.

The following outcomes will be measured:

The fMRI outcome measure and endpoint will be change in amygdala blood oxygen level-dependent (BOLD) response to emotional faces from baseline (Visit 2, pre-scan) to the second MRI scan performed 6 weeks following the initial dosing session (Visit 7). Differences in the BOLD response will be compared between subjects treated with psilocybin (Fig. 10A, condition 1) and subjects treated with escitalopram (Fig. 10A, condition 2).

The efficacy outcome measure and endpoint will be the change in QIDS-16 score from baseline (screening) to 6 weeks following the initial dosing session (Visit 7). QIDS-16 will also be performed one day before dosing and one day after dosing using a version of the scale tailored to daily use. After 6 weeks, QIDS-16 measures will be collected monthly up to 6 months post-dosing.

Differences in QIDS-16 score will be compared between subjects treated with psilocybin (Fig. 10A, condition 1) to subjects treated with escitalopram (Fig. 10A, condition 2). The criteria for determining response will be a reduction of 50% in QIDS-16 scores and remission will be scores of ≤5 on the QIDS-16.

Additional outcomes comprise a number of psychological assessments, including but not limited to patient (BDI) and clinician (HAM-D) depression rating scales, well-being (WEMWBS),

anxiety (STAI), optimism (LOT-R), and personality (BIG-5) scales and others described in Table 3D.

Additional outcomes also comprise imaging outcomes such as anatomical (e.g., morphometry, cortical thickness and tractography) and functional measures (e.g., cerebral blood flow, BOLD, resting-state functional connectivity, signal variance and entropy/complexity, and activations to emotional faces).

Psychological outcome measurements will be performed on subjects before (Visit 1) and after treatment (Visit 7) with either psilocybin or escitalopram. The different types of psychological outcome measurements are shown in Table 3C below.

Table 3C. Psychological Outcome Measurements

Test	Description	Reference
QIDS-16 (primary efficacy outcome measurement)	Measures internal states including most of the diagnostic criteria for depression. QIDS is sensitive to treatment effects.	Rush et al., *Biological Psychiatry.* 2003; 54(5):573-83; Cameron et al., *Journal of Psychiatric Research.* 2013; 47:592-8. Cameron, et al., *J Psychiatr Res*, 2013; 47:592-8.
QIDS-16 (daily)	Daily measurement of depression symptoms	Lenderking et al. Reliability, validity, and responsiveness of the QIDS-SR16 daily version. International Society of Quality of Life Research. (2005) Annual Meeting, San Francisco, CA.
Beck depression inventory (BDI II)	Self-reported inventory of depression severity	Beck et al. *Clinical psychology review*. 1988; 8(1):77-100.
Hamilton Depression Rating Scale (HAM-D)	Clinician-administered depression assessment	Hamilton, M. *Journal of Neurology, Neurosurgery & Psychiatry*. 1960; 23:56-62.
Montgomery-Asberg Depression Rating Scale (MADRS)	Unidimensional assessment of the symptoms of depression	Bech et al. *Neuropharmacology*. 1978; 17(6) 430-431.
Spielberger's Trait Anxiety Inventory (STAI)	Self-reported inventory that measures state anxiety and trait anxiety	Spielberger et al. Manual for the State-Trait Anxiety Inventory STAI. 1983.
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)	Measures the feeling and functioning aspects of mental wellbeing	Tennant et al. *Health and Quality of Life Outcomes*. 2007; 5:63.
Flourishing Scale (FS-8)	Summary measure of the subject's self-perceived success in areas such as relationships, self-esteem, purpose, and optimism	Diener et al. Assessing Well-Being, Social Indicators Research Series. 2009; 39: 247-266.

Snaith Hamilton Anhedonia Pleasure Scale (SHAPS)	Measures the presence of anhedonia, namely the inability to experience pleasure	Snaith et al. *The British Journal of Psychiatry.* 1995; 167:99-103.
Life Orientation Test (LOT-R)	10-item scale that measures how optimistic or pessimistic the subject feels about the future	Glaesmer, et al. *British Journal of Health Psychology*. 2012; 17:432-445.
Meaning in Life Questionnaire (MLQ)	10-item measure of the presence of meaning and search for meaning of life	Steger, et al. *Journal of Personality*. 2008; 76:199-228.
Brief Resilience Scale (BRS)	Measures the ability to recover from stress	Smith et al*. International Journal of Behavioral Medicine*. 2008; 15: 194-200.
Dysfunctional Attitudes Scale (DAS)	Self-report scale that measures the presence and intensity of dysfunctional attitudes	Weissman. The Dysfunctional Attitude Scale: A validation study. 1979.
44-item Big Five Inventory	Self-report questionnaire that measures extraversion, agreeableness, neuroticism, and openness to experience	John, et al. The Big Five Inventory—versions 4a and 54, Berkeley, CA: University of California, Berkeley, Institute of Personality and Social Research, 1991.
Peters 21-item delusional inventory (PDI)	Self-report that measures schizotypal traits and symptoms	Peters, et al. Measuring Delusional Ideation: the 21-item Peters et al. Delusions Inventory (PDI). Schizophrenia bulletin 30 (2004) 1005.
Examination of Anomalous Self-Experience (EASE)	Psychometric checklist to examine anomalies of subjective self-experience	Parnas, et al. *Psychopathology*. 2005; 38:236-258.
Ruminative Responses Scale (RRS)	Self-report measure of rumination comprising 10 items and two components: reflection and brooding	Treynor et al. *Cognitive Therapy and Research*. 2003; 27:247-259.
White Bear Suppression Inventory (WBSI)	15-item questionnaire that measures thought suppression	Wegner et al. *Journal of Personality*. 1994; 62:615-640.
Barrett Impulsivity Scale (BIS)	Questionnaire designed to assess the personality and behavioural construct of impulsiveness	Patton et al. *Journal of Clinical Psychology*. 1995; 51:768-774.
Brief Experiential Avoidance Questionnaire	Measures a broad range of experiential avoidance content	Gámez et al. Avoidance Questionnaire: Development and Initial Validation. *Psychological Assessment*. 2014; 26:35-45.
Modified Tellegen Absoprtion Questionnaire (MODTAS)	Self-report measurement of the subject's openness to experience, emotional and cognitive alterations across a variety of situations	Tellegen et al. *Journal of Abnormal Psychology*. 1974; 83:268.

Scale To Assess the Therapeutic Relationship (STAR)	Scale to measure therapeutic relationships between patients and clinicians in community mental health care settings	Mcguire-Snieckus et al. *Psychological Medicine*. 2007; 37:85-95.
Credibility/Expectancy Questionnaire	Scale for measuring treatment expectancy and rationale credibility for use in clinical outcome studies	Devilly et al. *Journal of Behavior Therapy and Experimental Psychiatry*. 2001; 31:73-86.
Connectedness to Nature Scale (CNS)	Measurement of individuals' trait levels of feeling emotionally connected to the natural world in the realm of social and environmental psychology	Nisbet et al. The nature relatedness scale: Linking individuals' connection with nature to environmental concern and behavior. Environment and Behavior (2008).
Political Perspective Questionnaire (PPQ)	Measures political attitudes	Nour et al., *Journal of Psychoactive Drugs*. 2017; 49(3):182-191.
Social Connectedness Scale (SCS)	Measures the degree to which the subject feels connected to others in their social environment	Lee et al. *Journal of Counseling Psychology*. 1995; 42:232.
Bech-Rafaelsen Mania Rating Scale (MAS/MRS)	Measures motor activity, verbal activity, flight of thoughts, voice/noise level, hostility/destructiveness, mood, self-esteem, contact with others, sleep changes, sexual interest, and work activities	Bech et al. *Neuropharmacology*. 1978; 17(6):430-431.
Revised Santa Clara brief compassion scale (SCBCS)	5-item scale that measures compassion and its link to prosocial behaviours	Hwang et al. Pastoral Psychology. 2008; 56: 421-428.
Gratitude Questionnaire (GQ-6)	6-item self-report questionnaire designed to assess individual differences in the proneness to experience gratitude in daily life	McCullough et al. *Journal of Personality and Social Psychology*. 2002; 82: 112.
Short Suggestibility Scale (SSS)	Self-report measure of the general tendency to accept messages	Kotov, S.B. Bellman, and D.B. Watson, Multidimensional Iowa Suggestibility Scale (MISS) Brief Manual. Stoneybrook Medicine website, 2004.
Rosenberg Self-Esteem Scale (RSE)	A scale that measures global self-worth by measuring both positive and negative feelings about the self	M. Rosenberg, Society and the adolescent self-image. 1965.
Universality Subscale of the Spiritual Transcendence Scale (STS)	Measures three core constructs related to spiritual transcendence: universality, prayer fulfilment, and connectedness	Piedmont et al. *Journal of Personality*. 1999; 67:985-1013.

Oxford Questionnaire on the Emotional Side-effects of Antidepressants (OQuESA)	Self-report measure of emotional symptoms present in patients treated with antidepressants	Price et al. *Journal of Affective Disorders*. 2012; 140 (2012) 66-74.
Lauks Emotional Intensity Scale (LEIS)	Measures selective serotonin reuptake inhibitor-induced emotional blunting	Opbroek et al., *International Journal of Neuropsychopharmacology*. 2002; 5:147-151.
The Suicidal Ideation Attributes Scale (SIDAS)	Measures the presence of suicidal thoughts and assesses the severity of suicidal thoughts	Van Spijker et al. *Suicide and Life-Threatening Behavior*. 2014; 44 (4): 408-419.
Sexual dysfunction (PRSEXDQ-SALSEX)	Questionnaire about libido, orgasm, ejaculation, erectile function and general sexual satisfaction	Montejo et al. *Journal of Sex Marital Therapy*. 2008; 34(3):227-39.
Selected items from Brief Index of Sexual Functioning for Women (BISF-W)	Measures female sexual function	Taylor et al. *Archives of Sexual Behavior*. 1994;23 (6) 627-643.
Sexual Perceptions Questionnaire (SPQ, self-constructed)	2-item questionnaire inquiring about whether individuals are open to trying new things in their sex life and whether they see sex as a sacred experience	
Barnes Akathisia Rating Scale (BARS)	Measures the severity of drug-induced akathisia or restlessness	Barnes et al. *Br J Psychiatry*. 1989; 154:672-6.
Work Productivity and Activity Impairment Questionnaire (WPAI)	Measures impairments in work and activities	www.rxlist.com/drug-interactions/serious-index/escitalopram-oral.htm
The Work and Social Adjustment Scale (WSAS)	Measures the subject's perceived functional impairment resulting from a health problem	Cooper et al. *Journal of Psychopharmacology.* 2015; 29(5):582-590.
Connectedness Questionnaire (self-constructed)	Measures interpersonal closeness and belonging with the social world	
Standard Assessment of Personality – Abbreviated Scale (SAPAS)	Short and simple screen for personality disorders	Moran et al. *The British Journal of Psychiatry.* 2003; 183(3):228-232.
Positive and Negative Syndrome Scale (PANSS)	Medical scale used for measuring symptom severity of patients with schizophrenia	Kay et al., *Schizophrenia Bulletin*. 1987; 13(2):261-76.
Mastery Insight Scale (MIS, taken from Therapeutic Realizations Scale)	Measures the sense of self-efficacy and the perception of an ability to cope and actively function to meet one's needs and goals	Kolden et al. *Journal of Clinical Psychology*. 2000; 56(9):1207-1220.

Self-Reflection and Insight Scale (SRIS)	Measures private self-consciousness	Grant et al. *Social Behavior and Personality*. 2002: 30(8), 821-836.
Psychological Insight Scale (PIS, self-constructed)	Questionnaire with an “insight” factor, including several items addressing how insightful the psychedelic experience was, and an “action” factor, addressing how much the patients have acted on these insights	
Metaphysical Beliefs Questionnaire (MBQ, self-constructed)	Questionnaire looking at different types of metaphysical-like beliefs that individuals can have before and after a psychedelic session	
Spiritual Bypassing Scale (SBS, self-constructed)	Questionnaire looking to address whether individuals who take psychedelics can bypass working through difficult issues and transcend into feeling "enlightened"	
Adverse Childhood Experience Questionnaire (ACE)	Questionnaire that evaluates different types of abuse, neglect, and other hallmarks of a rough childhood	Felitti et al. *American Journal of Preventive Medicine*. 1998:14(4) 245-355.
Therapeutic Music Experience Questionnaire (TMEQ, self-constructed)	Questionnaire looking at the effect of therapeutic music	
Setting Questionnaire (SQ, self-constructed)	Questionnaire looking at the effect of different setting elements on a psychedelic therapy session: the physical environment, the music and the guides	
Selected Items from the Absorption in Music Scale (AIMS - revised)	Measures the subjects’ ability and willingness to allow music to draw them into an emotional experience	

The assessments are intentionally brief and will take approximately 75 minutes to complete. Subjects will be encouraged to complete the assessments in two or more ‘stints’ and to take a break if they become tired and lose focus.

Outcomes Measured Immediately Before Treatment

The subject will complete a number of psychological assessments and behavioural tasks immediately before treatment with either psilocybin or escitalopram. A description of these outcome measurements are provided in Table 3D and Table 3E below.

Table 3D. Outcomes Measured Before Treatment

Scale	Description	Reference
Spielberger's Trait and Anxiety Inventory	Self-reported inventory that measures state anxiety and trait anxiety	Spielberger et al. Manual for the State-Trait Anxiety Inventory STAI. 1983.
Psychedelic Predictor Scale (self-constructed)	Questionnaire looking at the subject's mindset just before a psilocybin dosing session, how ready they feel to 'let go' and 'surrender' to the experience	
Surrender Scale (self-constructed)	Measures the willingness of a subject to "let go" and "surrender" to the experience	

Table 3E. Behavioural Tasks

Behavioural Task	Description	Reference
Emotional processing battery	Measures emotional processing, including facial expression recognition, emotional memory, attentional vigilance, and working and verbal memory	Cooper et al. *Journal of Psychopharmacology*. 2015; 29(5):582-590.
Cued autobiographical memory task (AMT)	Measures the degree of specificity of autobiographical memory	Williams et al. *Journal of Abnormal Psychology*. 1986; 95:144.
Prediction of Future Life Events (POFLE)	Measures the relationship between depressive symptoms and the bias in the prediction of future life events	Strunk et al. *Behavior Research and Therapy*. 2006; 44:861-882.
Torrance Test of Creative Thinking (TTCT)	Measurement to identify creatively gifted and talented individuals	Torrance, Torrance Tests of Creative Thinking, Personnel Press, Incorporated, 1968.
Emotional response to music	Assesses music-evoked emotional response	Kaelen et al. LSD enhances emotional response to music. *Journal of Psychopharmacology*. 2015; 232(19): 3607-3614
California Verbal Learning Test (CVLT)	Assessment of verbal learning and memory	Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A. California Verbal Learning

		Test: Adult version. Manual. Psychological Corporation, San Antonio, TX., 1987.
Digit Symbol Substitution Test (DSST)	Neuropsychological test sensitive to brain damage, dementia, age and depression	Jaeger, J. and Domingo S.Z. The Digit Symbol Substitution Test (DSST): psychometric properties and clinical utility in major depressive disorder. Poster presented at the 29th ECNP Congress, 17-20 September, 2016, Vienna, Austria.

Outcomes Measured During the Dosing Sessions

The subjective states of the subjects will be determined during the first and second dosing sessions (Visit 3 and Visit 5, respectfully). Table 3F lists the scales that will be used to measure subjective states.

Table 3F. Subjective State Scales

Subjective State Assessment	**Description**	**Reference**
Ego Dissolution Inventory (EDI)	Measurement of comprised sense of self	Nour et al. *Frontiers in Human Neuroscience*. 2016; 10:269.
Mystical Experience Questionnaire (MEQ)	Self-report questionnaire that measures hallucinogen-occasioned spiritual experiences	Barrett et al. *Journal of Psychopharmacology*. 2015; 29:1182-90.
11 Dimension Altered States of Consciousness Scale (11D ASC)	Measures altered states of consciousness	Studerus et al. PloS One. 2010; 5:e12412.
Psychotomimetic States Inventory (PSI)	Measures psychotic-typic experiences with sub-scales of delusory thinking, perceptual distortions, cognitive disorganization, anhedonia, mania and paranoia	Mason et al. *Schizophr Res*. 2008; 103:138-42.
Visual Analogue Scales (VAS)	Measures characteristics of disease-related symptom severity in individual patients for use in the classification of symptom severity and disease control	
Geneva Emotional Music Scales (GEMS)	Measures musically-evoked emotional responses	Zentner et al. *Emotion.* 2008; 8:494.

The Challenging Experience Questionnaire	Assesses challenging aspects of experiences with psilocybin	Barrett et al. The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. *Journal of Psychopharmacology*, 2016.
The Imperial Emotional Breakthrough Inventory (EBI)	Measures long-term emotional responses to psychedelic therapy	
Near-Death Experience (NDE) scale	Measures near-death experiences across time, culture and condition	B. Greyson. *The Journal of Nervous and Mental Disease*. 1983; 171:369-375.
Ten Item Personality Inventory (TIPI)	Measures five personality traits: extraversion. Agreeableness, conscientiousness, emotional stability, and openness	Cooper et al. *Journal of Psychopharmacology*. 2015; 29(5):582-590.

The subject's significant other will also be provided a short questionnaire at baseline and 6 weeks following the initial dosing session (Visit 7) to enquire how they perceive the subject's depression and whether they have noticed any changes in the subject's behaviour since the intervention. The Significant Other Questionnaire has 10 Likert scale items and will take approximately 10 minutes to complete. Subjects and their significant other will be made aware that this is not a compulsory part of the study procedure.

The subject will undergo several scanning outcome measures. Blood oxygen level dependent (BOLD) signal scans will be determined at resting state, in response to emotional faces, and with music as a hedonic stimulus. Anatomical scans (T 1 and T2) and diffusional tensor imagining (DTI) scans will also be performed.

After the 6 week primary end-point, subsequent follow-up will be performed remotely with the exception of a structured interview at 6 months.

Subjects

Subjects will be at least 18 years of age with an acceptable level of physical health as determined by a medical screening that includes routine blood tests, ECG, blood pressure and heart rate, neurological exam and psychiatric assessment. The initial screening procedure is described in Visit 1 above.

Subjects recruited for the study evaluating psilocybin versus escitalopram for MDD were enrolled based on the inclusion criteria shown in Table 3G below.

Table 3G. Study Inclusion Criteria

No.	Criteria
1	Major depressive disorder (DSM-IV)
2	Depression of moderate to severe degree (17+ on the 21-item HAM-D scale)
3	No MRI contraindications
4	No SSRI contraindications
5	A general practitioner or other mental healthcare professional that can confirm diagnosis
6	18-80 years of age
7	Males and females
8	Sufficiently competent with English language

Subjects recruited for the study evaluating psilocybin versus escitalopram for MDD will be excluded from the study based on the criteria shown in Table 3H below. In general, subjects with cardiovascular abnormalities, epilepsy, personal or family histories of psychosis or psychotic symptoms (including mania), or histories of suicide attempts, will not be allowed to participate in the study.

Table 3H. Study Exclusion Criteria

No.	Exclusion Criteria
1	Current or previously diagnosed psychotic disorder
2	Immediate family member with a diagnosed psychotic disorder
3	Medically significant condition rendering unsuitability for the study (e.g., diabetes, epilepsy, severe cardiovascular disease, hepatic or renal failure)
4	History of serious suicide attempts requiring hospitalization.
5	Significant history of mania (determined by study psychiatrist and medical records)
6	Psychiatric condition judged to be incompatible with establishment of rapport with therapy team and/or safe exposure to psilocybin, e.g. borderline personality disorder
7	Blood or needle phobia
8	Positive pregnancy test at screening or during the study, women who are planning a pregnancy and/or women who are nursing/breastfeeding.
9	Participants who do not agree to use an acceptable contraceptive method throughout their participation in study (see section 7.2.1).
10	Current drug or alcohol dependence
11	No email access
12	Use of contraindicated medication

13	Patients presenting with abnormal QT interval prolongation at screening or with a history of this (QTc at screening above 440ms for men and above 470ms for women)
14	History of serious suicide attempts requiring hospitalization.
15	Significant history of mania (determined by study psychiatrist and medical records)

Subjects receiving any of the medications shown in Table 31 will be asked to either discontinue the medication in an appropriate way, or may be excluded from the trial completely. Contraindicated medications for escitalopram are shown in Table 31 below.

Table 31. Contraindicated medications for escitalopram

Category	**Drug**
Monoamine oxidase inhibitors (MAOIs)	
Cancer medications	Procarbazine
NSAIDS	Aspirin and other drugs classified as NSAIDS
Cardiac medications	Class 1a (Quinidine, Procainamide, Disopromide) and Class III (Dofetilide, Ibutilide, Sotalol) Antiarrythmic drugs
Antihistamines	Terfenadine, Astemizole
Antipsychotics	Haloperidol, Droperidol, Thioridazine, Sertindole*, Ziprasidone, Risperidone, Zimeldine, Chlorpromazine
Antidepressants	Citalopram, Amitriptyline, Desipramine, Imipramine, Maprotiline, Doxepin, Fluoxetine
Antibiotics	Quinolone (Sparfloxacin, Levofloxacin, moxifloxacin, grepafloxacin) and Macrolide (Erythromycin, Clarithromycin)
Antimalarials	Quinine, Halofantrine
Antiprotozoal	Pentamidine
Antifungal	Azole group
Antimotility agents	Cisapride
Methadone	

Antipsychotic medications and mood stabilizers may attenuate the effects of psilocybin and so are also contraindicated for this reason. However, such medications are usually only prescribed for manic and/or psychotic illness, and subjects presenting with such histories would be excluded from the study.

Subjects that have previous experience with psychedelic drugs will be included in the study; however, it is anticipated that most subjects will not have previous experience with a psychedelic drug.

General practitioners will be contacted for each subject to inform them of the details of the clinical study and to enquire whether they have any concerns about their patient entering the trial. Subjects will not be allowed to enter the clinical study until we have confirmed their background medical and psychiatric history. Prior attitudes towards treatments will be collected and entered into the regression analysis. Psychiatric diagnosis is principally determined by one of our study psychiatrists, but confirmation will be sought for each subject from past and/or current practitioners. If confirmation of diagnosis is not initially forthcoming about a given subject, a decision will be made by the study clinical team on whether or not to enrol the subject.

The subject may withdrawal from the clinical study at any time or may be removed from the study under certain circumstances. Withdrawal criteria from the study includes: 1) withdrawal of consent; 2) development of concurrent physical illness that necessitates their removal; 3) deterioration of mental health warranting additional input and support; 4) dependency or problematic alcohol or illicit substance abuse; and 5) positive pregnancy test in women of childbearing potential at any point during study.

Upon entering the clinical study, if there is any deterioration in the subject's physical or mental health that may compromise their ability to continue in the trial then an informed decision will be made about whether their continued participation is prudent. This will all be done in discussion with the subject, the extended research team, and relevant health professionals.

Standard Operating Procedures for Adverse Events and Reactions

Adverse events (AEs) and adverse reactions (ARs), as well as drug-specific safety concerns, including side-effects, will be monitored and addressed if necessary during this study.

Prior to administration of psilocybin, the research team will fully prepare each study participant of what to expect in order to put the participant at ease with the process. Participants will also meet all members of the research team. This approach has been used in previous studies and is thought to significantly reduce the possibility of any psychological adverse events following administration of psilocybin because the subjects are comfortable within their surroundings and know what to expect from the study.

Subjects will be escorted and chaperoned by a member of the research team at all times throughout their participation in the study. For the period during which the subject will be under the acute effects of psilocybin, they will always be supported by research personnel.

The acute effects of psilocybin subside 5-6 hours following administration; however, the patient will be carefully monitored for the duration of their stay at the study centre.

We do not envisage any serious side-effects from administration of psilocybin; however, patients may experience anxiety reactions or paranoid thoughts. These are likely to be short-lived and will be managed by psychological approaches such as reassurance and adopting a calm and supportive manner and by using behavioural techniques such as guided imagery or breathing exercises.

Subjects will also be offered the opportunity for a member of the therapy team to provide reassuring "arm holding". During arm holding, a therapist will place their hand on the patient's wrist or arm, as a way of helping the subject feel secure during drug administration. Arm holding will have been previously practiced during the preparation session. Previous clinical studies with psilocybin has shown that many subjects reported feeling reassured by having the option of arm holding if they felt anxious.

In the unlikely event that a patient becomes behaviourally disturbed, and the use of de-escalation techniques are not sufficient, medical personnel from the research team will be on hand to administer tranquillisation if necessary, i.e., lorazepam. Subjects will be asked to consent to possible administration of lorazepam before dosing. Typical doses initially administered would be 1-2 mg lorazepam perorally then titrated to effect. Tranquilizing medication will only be used in extreme circumstances.

If such an adverse event occurs, a member of the staff will accompany the subject at all times and in no circumstances will they be permitted to leave the unit until the psychiatrist is satisfied that they are in a fit state to do so.

We anticipate that the majority of subjects will return home approximately 6 hours after receiving psilocybin; however, there may be subjects who are not in the appropriate frame of mind to be discharged from the clinical research facility at that time. In the event that this occurs, a psychiatrist will remain in the department for as long as is necessary to ensure that the subject recovers to their previous level of functioning.

Prior to a subject's discharge from the unit, an assessment of their current level of risk will be conducted to determine whether it is safe for them to leave. If there are any reservations about discharging a subject, they will be offered the option of an overnight stay at a nearby facility until the following day. They will be supported overnight by the psychiatrist and research nursing staff. Subjects will then be reviewed the next morning to establish whether they have returned to their normal level of functioning and it will be decided whether or not they can return home.

We will ask that the subject have a friend or family member at home when they return. We will ask for their contact details so that we can contact them if we cannot manage to contact the subject themselves.

Subjects who do not have a chaperone at home will be encouraged to take advantage of the onsite accommodation.

Phone numbers for each member of the research team will be provided to the subject and their chaperone to ensure immediate contact if required. The contact details for the patient and their responsible other will also be provided to the research team. Twenty-four-hour emergency contact numbers will be provided.

Appropriate follow-ups are in place for monitoring the subject's status throughout the study and afterwards. We will therefore be able to detect any prolonged or delayed adverse events.

Subjects and their relatives will be encouraged to contact the research team should their mental or physical health deteriorate. Although our options of managing their current difficulties will be limited after the study is complete, we will be able to offer referral to relevant services. If indicated, we will offer a further follow-up at the clinical research facility so that we can review the subject in person.

Drug-Specific Safety Considerations

Psilocybin Safety:

Subjects treated with psilocybin (Fig. 10A, condition 1) will be monitored for adverse side effects. Common and rare side effects of 25 mg psilocybin are provided in Table 3J.

Table 3J. Side Effects of Psilocybin

Frequency	Side Effects
Common (>20% at 25 mg psilocybin)	Increased anxiety, particularly at onset of the drug; mild-moderate increased heart rate; visual hallucinations; transient headaches, lasting for 1 to 2 days after dosing
Less common (<15% at 25 mg psilocybin)	Paranoia or suspiciousness; nausea; dizziness; a "bad trip" characterized by negative thoughts and mood during acute drug effects
Rare (prevalence unknown but likely <2%)	HPPD/flashbacks; worsening of mental state after drug experience;

It is not uncommon for people to experience some negative psychological content during a psilocybin 'trip', particularly if they suffer from ongoing psychological distress, as is characteristic of depression. Typically, this is best dealt with by good preparation and support during the

experience and integration afterwards. In previous clinical studies with psilocybin, challenging episodes were relatively common within the patients' trips; however, none were entirely characterized by dysphoric or distressing content. When challenging content did arise, it was often worked through and contributed to a psychological 'breakthrough' on the part of the subject. Recent evidence indicates that challenging psychological experiences can produce therapeutic benefits, such as improved psychological well-being in the long-term.

Negative aftereffects of challenging psychological experiences under psychedelics are thought to be a consequence of inadequate 'set and setting' and post-session integration work - and they may also relate to the duration of the challenging period. The present clinical study aims to reduce these risks through psychological preparation and integration work, good patient-staff rapport and a positive environment.

Research and medical staff will also plan carefully for challenging experiences. These episodes are best managed psychologically; however, in cases of severe panic that is unresponsive to psychological intervention, injectable lorazepam will be available for use as a "rescue medication". Consent for such medication will be sought from the subject ahead of study participation. Detailed protocols are available on the safe management of clinical research with psychedelics.

Escitalopram Safety:

Subjects treated with escitalopram (Fig. 10A, condition 2) will be monitored for adverse side effects. As with all selective serotonin reuptake inhibitors, side effects of escitalopram are commonly reported. Common and rare side effects of 20 mg escitalopram are provided in Table 3K below.

Table 3K. Side Effects of Escitalopram

Frequency	Side Effects
Common (~10% at 20 mg escitalopram)	Agitation or restlessness; diarrhea; difficulty sleeping; drowsiness; dry mouth; headache; nausea; sexual difficulties (decreased sexual ability or desire, ejaculatory delay); dizziness; sweating
Less common (<10% at 20 mg escitalopram)	Frequent urination; indigestion; increased or decreased appetite; taste alterations; tremor (shaking); tingling in arms or legs; weight changes; influenza-like symptoms and pain in neck or shoulders; serotonin syndrome; suicidal thinking and behaviour; abnormal bleeding; seizures; manic episodes; low sodium; angle closure glaucoma

In the event of signs of cardiac arrhythmia (e.g., fluttering in chest, tachycardia, bradycardia, chest pain, shortness of breath, and lightheadedness), subjects will be advised to stop escitalopram dosing and contact the research personnel and their general practitioner immediately. Under these circumstances, the subject will undergo an additional visit and perform an extra ECG to evaluate heart function.

After completion of the study, the study psychiatrist will conduct individual consultations with patients treated with escitalopram (Fig. 10A, condition 2) to discuss whether they would like to continue with escitalopram or return to treatment as usual after controlled withdrawal. Gradual withdrawal from escitalopram will be managed by the study psychiatrist in consultation with the patient's general practitioner or psychiatrist in order to prevent antidepressant discontinuation syndrome.

Example 5. Clinical Study Examining Psilocybin for the Treatment of Treatment-Resistant Depression

Studies with more rigorous designs are needed to better the therapeutic potential of psilocybin in treatment-resistant depression (TRD). The aim of this study is to assess the effectiveness of 3 different doses of psilocybin (1 mg, 10 mg, and 25 mg) in TRD.

This is a Phase 2b, international multicentre, randomized, fixed dose, double-blind trial. The study population will include adult men and women, 18 years of age and older, with TRD. Subjects 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; if single episode MDD, the duration of the current episode must be at least 3 months but not more than 2 years. Augmentation counts as a second treatment, provided it is approved for the adjunctive treatment of MDD in that country.

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

The majority of subjects will have no prior exposure to psilocybin or so-called magic mushrooms; however, to reflect the prevalence of experience in general population, we will allow up to 10% of subjects with prior recreational experience with psilocybin or magic mushrooms. Past exposure to psilocybin has to be more than 12 months prior to screening and not during the current depressive episode. This will be constrained by the centralized randomization process, Interactive Web-based Response System.

Subjects 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 (HAM-D-17), the Massachusetts General Hospital Antidepressant Treatment History Response Questionnaire (MGH-ATRQ), the Columbia-Suicide Severity Rating Scale (C-SSRS), and McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). Those who meet the eligibility criteria will enter the screening period which will last between 3 and 6 weeks. At the initial screening visit (Visit 1), the subject will also be evaluated with the 16-Item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16), and the Adult Self Report Scale (ASRS). Additionally, a medical history, an electrocardiogram (ECG), blood tests, and vital signs will be obtained.

Subjects taking antidepressant medications will have tapered their use at least 2 weeks prior to baseline (Visit 2). Eligible subjects will be invited for a screening visit (Visit 1a). Visit 1a is the point at which the subject begins tapering off their antidepressant and/or antipsychotic medications, if appropriate. The subject must complete the taper within the first 4 weeks of this period, prior to 2 weeks completely off antidepressant and/or antipsychotic medications, before baseline Visit 2. The tapering period used in the study is set at the industry standard for depression trials.

All subjects will be evaluated for safety at the clinic weekly for a minimum of 3 weeks prior to psilocybin administration to ensure safe discontinuation of current antidepressant therapy required by the protocol. Subjects' companions (friend or family member) will be educated about the signs of worsening of depression and suicidality, and instructed on ways to contact the study team in case of significant worsening of depression. Any safety assessment visits during the screening period will be called Visit 1a, Visit 1b, 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 subject 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 subject will review psychoeducational materials provided at the time of enrolment.

The day before the psilocybin session, the subjects will undergo a baseline assessment (3 to 6 weeks after initial screening [Visit 1]) that will consist of the HAM-D-17, MADRS, QIDS-SR-16, C-SSRS, SDS, GAD-7, DSST, EQ-5D-3L (administered to both subject and caregiver [the latter is not mandatory]), WSAS, vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential). Both the therapist and the subject will be asked to

fill out a therapeutic alliance evaluation questionnaire, STAR-C and STAR-P, respectively. After baseline data is entered into EDC, the CAT team will complete a final review to ensure the subject's continued eligibility. Subjects cannot be progressed to Visit 3 until this approval is received.

The psilocybin administration session (Visit 3, Day 0) will last approximately 6 h and will be supported by a trained therapist. Psilocybin sessions may be video recorded for training and adherence monitoring. After the acute effects of the psilocybin pass, subjects will be evaluated for safety and accompanied home. On Day 1 (Visit 4), the day following psilocybin administration, subjects 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 subject may be audio recorded for adherence monitoring and quality assurance. Audio and video recording of the sessions are subject to subject consent. Subjects who do not consent to either or all recordings will not be excluded from the study.

All subjects will be asked to remain off their antidepressant medications for at least 3 weeks following the psilocybin session until the primary endpoint assessment, or longer. Rescue medications are allowed and described in the Rescue Medications section below. Subjects who restart their antidepressant medications during the first 3 weeks after the psilocybin treatment administration will be assessed for reasons of resuming their medications and followed until 12 weeks post-psilocybin administration.

The treatment period will determine the optimal therapeutic dose; 216 subjects will be randomised in a 1:1:1 ratio to receive 1 mg psilocybin, 10 mg psilocybin, or 25 mg psilocybin.

Subjects will be seen at the clinic for screening (Visit 1, plus a minimum of 3 safety visits), baseline (Visit 2, day -1), day 0 (Visit 3, Dosing), day 1 (Visit 4), Week 1 (Visit 5), Week 2 (Visit 6), Week 3 (Visit 7), and Week 12 (Visit 10). Subjects will also be contacted for follow-up at Week 6 (Visit 8) and Week 9 (Visit 9). The MADRS will be done by telephone and the other assessments will be done electronically. Subjects are seen at the clinic for safety visits between the initial screening (Visit 1) and the baseline (Visit 2) visit, and the visits will be labelled Visit 1a, Visit 1b, Visit 1c, etc.

The study schematic is shown in Fig. 11 and the schedule of assessments are presented in Table 4A below.

Table 4A. Schedule of Assessments

		3-6 weeks prior to Baseline			Time Post Psilocybin Session						
	Screen Visit[2]	Screening Period	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21	Week 6 Day 42	Week 9 Day 63	Week 12 Day 84 (ET)[3]
Visit	1	1a, 1b, etc.	2	3	4	5	6	7	8	9	10
Location of Visit[1]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote	Remote	Clinic
Allowable Window		Weekly		≤ 7 days	none	±1 day	±1 day	± 1 day	± 3 days	± 3 days	± 7 days
Clinic Assessments and Procedures											
Informed Consent	□										
Medical History	□		□								
Inclusion/exclusion Criteria	□		□								
MINI	□										
HAM-D-17	□		□								
MGH-ATRQ	□										
STAR-C			□								
C-SSRS4	□	□	□	□	□	□	□	□	□	□	□
Vital signs	□		□	□	□						
Weight	□										

		3-6 weeks prior to Baseline			Time Post Psilocybin Session						
	Screen Visit[2]	Screening Period	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21	Week 6 Day 42	Week 9 Day 63	Week 12 Day 84 (ET)[3]
Visit	1	1a, 1b, etc.	2	3	4	5	6	7	8	9	10
Location of Visit[1]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote	Remote	Clinic
Allowable Window		Weekly		≤ 7 days	none	±1 day	±1 day	± 1 day	± 3 days	± 3 days	± 7 days
Height	□										
ECG	□				□						
Clinical laboratory tests and biomarker[5]	□				□			□			
Urinalysis[5]	□				□						
Urine Drug Screen[5]	□		□								
Urine Pregnancy Test[6]	□		□								
Documentation of Birth Control to be used[7]	□										
2a polymorphism (optional)	□										

		3-6 weeks prior to Baseline			Time Post Psilocybin Session						
	Screen Visit[2]	Screening Period	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21	Week 6 Day 42	Week 9 Day 63	Week 12 Day 84 (ET)[3]
Visit	1	1a, 1b, etc.	2	3	4	5	6	7	8	9	10
Location of Visit[1]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote	Remote	Clinic
Allowable Window		Weekly		≤ 7 days	none	±1 day	±1 day	± 1 day	± 3 days	± 3 days	± 7 days
Activate/deactivate Mindstrong (optional)	□										□
Provide access to psychoeducational material (Longboat)	□	□[10]									
Psilocybin dose				□[11]							
Prior/Concomitant Medications	□	□	□	□	□	□	□	□	□	□	□
AE/SAE				□	□	□	□	□	□	□	□
Randomization			□								
Subject Completed Assessments											
5D-ASC				□[8]							
ASRS	□										

		3-6 weeks prior to Baseline			Time Post Psilocybin Session						
	Screen Visit[2]	Screening Period	Baseline (Day -1)	Psilocybin Session (Day 0)	Day 1	Week 1 Day 7	Week 2 Day 14	Week 3 Day 21	Week 6 Day 42	Week 9 Day 63	Week 12 Day 84 (ET)[3]
Visit	1	1a, 1b, etc.	2	3	4	5	6	7	8	9	10
Location of Visit[1]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote	Remote	Clinic
Allowable Window		Weekly		≤ 7 days	none	±1 day	±1 day	± 1 day	± 3 days	± 3 days	± 7 days
DSST			□		□			□			□
EBI					□						
EQ-5D-3L[9]			□					□			□
GAD-7			□					□			□
MSI-BPD	□										
PANAS			□		□			□			
QIDS-SR-16	□		□	□	□	□	□	□	□	□	□
SDS			□					□			□
STAR-P			□								
WSAS			□					□			□
Remote-rater Assessment											
MADRS			□		□	□		□	□	□	□

Abbreviations: 5D-ASC, Five Dimension Altered States of Consciousness Questionnaire; AE, adverse event; ASRS, Adult Self-Report Scale; CRP, C-reactive protein; C-SSRS, Columbia-Suicide Severity Rating Scale; DSM-5 Diagnostic and Statistical Manual of Mental Disorders (5th edition);DSST, Digit Symbol Substitution Test; EBI, Emotional Breakthrough Inventory; ECG, electrocardiogram; EQ-5D, EuroQoL 5-dimension; ET, early termination; GAD-7, Generalized Anxiety Disorder 7; h, hour(s); HAM-D-17, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Scale; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment History Questionnaire; MINI, Mini International Neuropsychiatric Interview; 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; SAE, serious adverse event; SDS, Sheehan Disability Scale; STAR-C, Scale to Assess the Therapeutic Relationship-Clinician; STAR-P, Scale to Assess the Therapeutic Relationship-Patient; UK, United Kingdom; VAS, visual analogue scale; WSAS, Work and Social Adjustment Scale

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

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

[4] The "Last 12 Months" version will be administered at Screening and the "Since Last Visit" version will be administered at all other visits.

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

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

[7] Site is to document method of contraception agreed to be used by each subject.

[8] To be administered immediately after the psilocybin session.

[9] The EQ-5D-3L will be administered to both the subject and their caregiver (latter is not mandatory).

[10] Blood pressure Longboat access can be granted at V1 or V1a at the study team's discretion.

[11] After baseline data is entered into EDC the CAT team will complete a final review to ensure the subject's continued eligibility. Subjects cannot complete psilocybin dose at V3 until this approval is received.

[12] Screening period visits should not be initiated until initial MM and CAT approval is received. Screening visits are to occur weekly 3-6 weeks prior to Baseline, number of visits is determined by the length of the subject's taper off antidepressant medication.

Instruments (all measures below will be captured electronically):

5D-ASC - The Five Dimension Altered States of Consciousness Questionnaire measures the acute drug effects.

ASRS - The Adult Self-Report Scale is a tool to screen for attention deficit hyperactivity disorder. The 6-item screener version will be administered.

C-SSRS - Columbia-Suicide Severity Rating Scale assesses treatment-emergent suicidal thoughts. This scale should be administered prior to dosing, if possible.

DSST - The Digit Symbol Substitution Test is a measure of cognition. It consists of a number of digit-symbol pairs, and requires individuals to note the corresponding symbol for a given digit under time-limited conditions. This test should be administered at approximately the same time of day each time to minimize the impact of diurnal variation on the results

EBI - The Emotional Breakthrough Inventory is an 8-item brief measure intended to index the degree to which an individual experiences his/her emotion during a psilocybin session. It is a VAS style scale, typically with units from 0 to 100. It is typically rated within 24 h of a psychedelic experience and ideally within 5 h of the 'end' of the psychedelic experience or once acute drug effects have significantly subsided.

EQ-5D-3L - The 3-level EQ-5D version (EQ-5D-3L) was introduced by the EuroQoL Group in 1990. The EQ-5D-3L essentially consists of 2 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 Generalized Anxiety Disorder scale is a 7-item subject completed scale to assess anxiety in a subject.

MADRS - the Montgomery-Asberg Depression Scale is a clinician rated outcome measure to assess a subject's level of depression.

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 scale is a subject-rated scale to assess their depression.

SDS - The Sheehan Disability Scale is a patient-reported outcome measure used to assess functional impairment and associated disability.

STAR-C and STAR-P -Scale to Assess the Therapeutic Relationship completed by the clinician (STAR-C) and the patient (STAR-P) to assess the therapeutic relationship in community psychiatry with good psychometric properties suitable for both research and routine care.

WSAS - Work and Social Adjustment Scale is a self-report scale used to assess psychosocial functioning and to predict durability of response to antidepressant treatment.

Study Objectives

The primary objective of this study is to evaluate the efficacy of psilocybin (25 mg or 10 mg) compared to 1 mg, administered under supportive conditions to adult subjects with TRD, in improving depressive symptoms, as assessed by the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline. Baseline is defined as the assessment score obtained on Day -1. The primary time point is week 3; this variable will be analyzed for the change from Baseline to day 1, and weeks 1, 3, 6, 9, and 12 of the study.

Additional objectives of this study are to assess the efficacy of psilocybin compared to 1 mg psilocybin on the:

(a) proportion of subjects with response defined as a ≥ 50% decrease in MADRS total score from baseline to week 3. This will also be assessed at day 1 and at weeks 1, 6, 9, and 12 of the study.

(b) proportion of subjects who have a sustained response at week 12. Sustained response is defined as the proportion of patients fulfilling response criteria at any visit up to and including week 3, that also fulfils response criteria at all subsequent visits up to and including week 12. Response is defined as ≥ 50% decrease in MADRS total score from baseline.

Another objective is to evaluate the safety and tolerability of psilocybin in subjects with TRD based on AEs, changes in vital signs, and suicidal ideation/behaviour (measured using the Columbia-Suicide Severity Rating Scale [C-SSRS]) score at all visits.

Other objectives are to evaluate the effects of psilocybin on quality of life and wellbeing, functioning and associated disability, cognitive function, and anxiety compared to 1 mg psilocybin on:

(a) Quality of life in subject EuroQoL (EQ)-5 dimension-3 level scale (EQ-5D-3L) score change from Baseline to week 3. This will also be assessed at week 12. This assessment is not mandatory.

(b) Quality of life in caregiver EQ-5D-3L score change from Baseline to week 3. This will also be assessed at week 12.

(c) Functioning and associated disability in the Sheehan Disability Scale (SDS) score change from Baseline to week 3. This will be also assessed at week 12.

(d) Cognitive function as measured by the Digit Symbol Substitution Test (DSST) score change from baseline to week 3. This will also be assessed at day 1 and week 12.

(e) Level of anxiety as measured using the change in Generalised Anxiety Disorder 7 item Scale (GAD-7) total score change from baseline to week 3. This will also be assessed at week 12.

(f) Subject determined level of depression as measured using the change in Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR-16) total score from Baseline to week 3. This will also be assessed at screening, day 1, and weeks 1, 2, 6, 9, and 12.

(g) Psychosocial functioning and predictor of response durability as measured using the change in Work and Social Adjustment Scale (WSAS) from Baseline to week 3. This will also be assessed at week 12.

(h) To evaluate the impact of different psilocybin doses on real life functional activity estimated from passive data streams collected on a mobile app on subjects' mobile phones. The data collected from the subject's phone will include: i) number of and time of phone calls/e-mails/texts; ii) gestures used (taps, swipes, other); iii) gyroscope (orientation) of the phone (the way the phone is pointing); iv) acceleration of the phone (sudden movements of the phone); v) keystroke patterns with characters redacted; location information from the GPS; and vi) the app also maintains a histogram of daily words that the subject types on their phone. These words will be stripped from their context and syntax, thus preventing the content of any particular message from being deciphered.

(i) Positive and Negative Affect Schedule (PANAS), Five Dimension Altered States of Consciousness Questionnaire (5D-ASC), 2a receptor polymorphism test and Scale to Assess Therapeutic Relationship (Clinician and Patient version, STAR-C and STAR-P, respectively) will be assessed for correlation with the primary and secondary outcomes as possible predictors of response.

The study endpoints are listed in Table 4B below.

Table 4B. Study Endpoints

Study Endpoint	**Assessments**
Primary	MADRS total score from baseline (day -1) to 3 weeks post-psilocybin
Secondary	a) The proportion of subjects with a response (defined as a ≥ 50% improvement in MADRS total score from Baseline) at week 3 after the psilocybin session. b) The proportion of subjects with remission (defined as a MADRS total score ≤ 10) at week 3 post psilocybin. c) The proportion of subjects who have a sustained response at week 12. Sustained response is defined as the proportion of patients fulfilling response criteria at any visit up to and including week 3, that also fulfils response criteria at all subsequent visits up to and including

	week 12. Response is defined as ≥ 50% decrease in MADRS total score from baseline. d) Time to event measures: restart antidepressant medication for any reason, restart medication for continuing depressive symptoms, and relapse from a previously recovered state (clinical judgement, supported by the QIDS-SR-16). Subjects who withdraw from the study will be censored from the time to event analysis.
Exploratory	Change from baseline in the following: a) Subject EQ-5D-3L at Week 3; b) Caregiver EQ-5D-3L at Week 3 (this assessment is not mandatory); c) SDS at Week 3; d) DSST at Week 3; e) GAD-7 at Week 3; f) QIDS-SR-16 at Week 3 g) WSAS at Week 3; and h) Measures derived from smart phone usage via the Mindstrong app.
Efficacy and Outcome	MADRS, SDS, QIDS-SR-16, GAD-7, DSST, EQ-5D-3L (subject and caregiver), WSAS

Study Procedures by Time Point

The study timeline includes 10 visits over a period of 12 weeks to assess the effects of psilocybin on TRD. The screening assessments for each Visit are listed in Table 4A.

Visit 1: Screening Period

The subject will be screened to evaluate suitability for the study. All subjects will be seen at the clinic weekly for a minimum of 3 weeks prior to baseline (Visit 2) to ensure safe discontinuation of current antidepressant therapy required by the protocol, and to conduct psychoeducation.

At the screening visit, a number of assessments shown below in Table 4A 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 subject-rated assessments throughout the study will be captured electronically.

If the subject is deemed eligible, they can proceed to the next visit (Visit 1a). Subjects cannot begin psychoeducation or tapering off their antidepressant medication until they attend the clinic for the screening visit (Visit 1a).

At subsequent screening period visits (Via, V 1b, etc.), medications taken and any changes in medications since the previous visit, and the C-SSRS will be obtained.

Visit 2: Baseline Visit - Day -1

The baseline visit should occur 3 to 6 weeks after initial screening (Visit 1). At the baseline visit, the subject's eligibility will be confirmed by reviewing the Inclusion/Exclusion criteria and updating the medical history. The baseline visit should occur the day before the anticipated psilocybin session. The following assessments performed at the baseline visit are shown in Table 4A.

If the subject continues to meet the eligibility criteria, the trained therapist will review the psychoeducational material and the anticipated psilocybin session with the subject. The subject will be randomized into the appropriate study group, i.e., 1 mg, 10 mg, or 25 mg psilocybin. using the IWRS (Section 8.2) and will return to the study site for treatment the following day. The research team will complete a final review to ensure the subject's continued eligibility. Subjects cannot be progressed to Visit 3 until this approval is received.

Visit 3: Psilocybin Session - Day 0

The psilocybin session (Visit 3) should occur the day after the baseline visit (Visit 2). In exceptional circumstances the subject may visit the clinic ≤ 7 d following the baseline visit (Visit 2). 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 (Visit 2). If the subject is out of the ≤ 7-day window, all baseline assessments are to be repeated, except randomization. The assessments provided at the psilocybin session are listed in Table 4A.

Visit 4: Post-dosing Day 1

The day after treatment the subject will return to the study site for a safety check and to discuss their experience during the psilocybin administration session. During this visit subjects will be reminded at this dosing session to remain off any antidepressant medications until after Visit 7. The assessments provided at post-dosing session are listed in Table 4A.

Visit 5: 1 Week Post-dosing

The subject will visit the clinic 1 week (7 days ± 1 day) following psilocybin administration. During this visit, subjects will be reminded to remain off any anti-depressant medications until after Visit 7. The assessments obtained during Visit 5 are shown in Table 4A.

Visit 6: 2 Weeks Post-dosing

The subjects will visit the clinic 2 weeks (14 days ± 1 day) following psilocybin administration. During this visit, subjects will be reminded to remain off any anti-depressant medications until after Visit 7. The assessments obtained during Visit 6 are shown in Table 4A.

Visit 7: 3 Weeks Post-dosing

The subjects will visit the clinic 3 weeks (21 days ± 1 day) following psilocybin administration. During this visit, subjects will be reminded to remain off any anti-depressant medications until after Visit 7. The assessments obtained during Visit 7 are shown in Table 4A.

Visit 8: 6 Weeks Post-dosing

The subject will be contacted by telephone by site staff or visit the clinic at the investigator's discretion 6 weeks (42 days ± 3 days) following psilocybin administration. All clinician or subject-rated assessments shown in Table 4A will be captured electronically.

Visit 9: 9 Weeks Post-dosing

The subject will be contacted by telephone 9 weeks (63 days ± 3 days) following psilocybin administration. The assessments obtained 9 weeks post-dosing are shown in Table 4A.

Visit 10: 12 Weeks Post-dosing (End of Study)

The subjects will visit the clinic 12 weeks (84 days ± 7 days) following psilocybin administration for the end of study visit. This visit is also to be completed if the subject is discontinued from the study early (early termination [ET]). The assessments obtained during Visit 10 are shown in Table 4A.

Description of Study Procedures

Efficacy, safety, and other types of assessments performed during the study are described in Tables 4C-E below. All measures below will be captured electronically.

Table 4C. Efficacy Assessments

Montgomery-Asberg Depression Rating Scale (MADRS)	MADRS evaluations will be performed by an independent remote rater who is blinded to the subject's treatment assignment at baseline, day 1, and weeks 1, 3, 6, 9, and 12. 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. The structure of the telephone-based interview will be controlled through the use of The Structured Interview Guide for the MADRS (SIGMA), which provides structured probes to ensure standardization of administration and comprehensive coverage of 10 questions.

Quick Inventory of Depressive Symptomatology	The 16-item QIDS-SR-16 a self-rated scale designed to assess the severity of depressive symptoms in the nine diagnostic symptom domains of a major depressive episodes, exclusive of atypical or melancholic symptoms. The QIDS-SR-16 is sensitive to change with various treatments, demonstrating its utility in research settings. The total score ranges from 0 to 27 with 0 representing no depression and 27 representing severe depression. The total score is the sum of the 9 symptom domains. The QIDS-SR-16 will be collected at every clinic visit or contact with the subject.
Sheehan Disability Scale	The SDS is a brief, 5-item self-report inventory that assesses functional impairment in work/school, social life, and family life. The total score ranges from 0 to 30 with 0 representing no impairment and 30 representing severe impairment. The last two items of the scale (Days Lost and Days Unproductive) do not count toward the total score. Each domain is rated on a 10-point visual analogue scale (VAS). The SDS will be obtained at baseline, and weeks 3 and 12.
Generalized Anxiety Disorder Scale	The GAD-7 is useful in primary care and mental health settings as a screening tool and symptom severity measure for the seven most common anxiety disorders. 32 Subjects choose one of 4 severity scores associated problems related to the common anxiety disorders and then indicate the degree to which these problems caused functional and/or social difficulties. Scores are determined by calculating the values for each column. A total score is obtained by the sum of all total column values. The GAD-7 will be obtained using the ePRO device at Baseline, and weeks 3 and 12.
Digit Symbol Substitution Test	The DSST is a neuropsychological test sensitive to brain damage, dementia, age and depression. The DSST consists of digit-symbol pairs followed by a list of digits. The subject will select the corresponding symbol as fast as possible. The number of correct symbols within 90 seconds will be recorded at baseline, day 1, and weeks 3 and 12.

EuroQoL-5 Dimension-3 Level Scale	The 3-level EQ-5D version (EQ-5D-3L) was introduced by the EuroQoL Group in 1990. The EQ-5D-3L essentially consists of 2 pages: 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 3 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The subject 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 subject's health state. The EQ VAS records the subject's self-rated health on a vertical 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 subject's own judgement. The EQ-5D-3L will be obtained at baseline, and weeks 3 and 12. Administration to a caregiver is not mandatory.
Work and Social Adjustment Scale	The WSAS is a 5-item self-report scale used to assess psychosocial functioning and to predict durability of response to antidepressant treatment. Each of the 5 questions is rated on a scale from 0 to 8, where 0 is no impairment and 8 is very severe impairment. A WSAS score above 20 appears to suggest moderately severe or worse psychopathology. Scores between 10 and 20 are associated with significant functional impairment but less severe clinical symptomatology. Scores below 10 appear to be associated with subclinical populations. The WSAS will be performed at baseline and weeks 3 and 12, and will be captured electronically.

Table 4D. Safety Assessments

Columbia-Suicide Severity Rating Scale (C-SSRS)	The C-SSRS will be used to assess suicide potential or tendency as a study entry criteria and monitored throughout the study. The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior over a specified time period. The

	measurement of suicidal ideation is based on 5 “yes” or “no” questions with accompanying descriptions arranged in order of increasing severity. If the patient answers “yes” to either questions 1 or 2, the intensity of ideation is assessed in 5 additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behavior is assessed by asking questions categorizing behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. If any item(s) on the C-SSRS are answered “yes”, the primary investigator or physician investigator must review the patient’s responses in order to (a) at screening and Baseline determine the patient’s study eligibility and potential need for referral to a mental health professional, and (b) during the study evaluate the patient’s need for appropriate medical management such as a referral to a mental health professional. A significant risk of suicide is defined as a “yes” in answer to (a) questions 4 or 5 on the suicidal ideation section; or (b) any questions on any item in the suicidal behavior section. This must be reported as an SAE and followed up accordingly. Additionally, if a patient responds “yes” to any of the suicidal ideation questions 1 through 3, the investigator should apply clinical judgment to determine the need for reporting this as an AE or SAE and the need for any appropriate referral.
Vital Signs	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. Respiratory rate, body temperature, and pulse rate will be obtained at screening, baseline, day 0, and day 1.
Electrocardiogram	Standard 12-lead ECGs will be obtained at screening (Visit 1) and day 1 (Visit 4).

Clinical Laboratory Tests	Blood samples will be obtained at screening (Visit 1), day 1 (Visit 4), and week 3 (Visit 7) for the following: a) *Hematology*: hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count (with differential), and platelet count. b) *Chemistry*: albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (direct, indirect, and total), calcium, chloride, creatine kinase, creatinine, gammaGT, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, protein-total, sodium, urea (blood urea nitrogen), and uric acid. c) *Biomarker*: C-reactive protein. d) *Other*: 2a polymorphism at screening (Visit 1) only (optional). Urine samples will be obtained at screening (Visit 1) and baseline (Visit 2) for the following: a) *Urinalysis*: A dipstick urinalysis will be performed for blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, and urobilinogen. b) *Urine Drug Screen*: for illicit drugs or drugs of abuse at screening (Visit 1) and baseline (Visit 2). Results of a positive drug screen will be reviewed by the study clinician for pattern of use. c) *Urine Pregnancy Test*: a dipstick test in women of childbearing potential at screening (Visit 1) and baseline (Visit 2).
Adverse Events	All AEs occurring after the subject signs the ICF and up to the last study event will be recorded. Any AEs occurring before the start of treatment (i.e., before the dose of the IP on day 0 [Visit 3]) will be recorded in the medical history. Any AE ongoing at Visit 10 (EOS/ET) will be followed until resolution or no longer considered clinically significant by the investigator.

Table 4E. Other Assessment Instruments

Hamilton Depression Rating Scale (HAM-D)	The HAM-D 17-item scale is used to measure the degree of symptom severity in depressed patients. The HAM-D-17 rating will be performed by the investigator using the eCOA device at the screening (Visit 1) and baseline (Visit 2) 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. This will be captured electronically.
Mini International Neuropsychiatric Interview (MINI)	The MINI was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-5 and International Classification of Diseases-10. Validation and reliability studies have been done comparing the MINI to the Structured Clinical Interview for DMS-5 Patient Edition and the Composite International Diagnostic Interview (a structured interview developed by the World Health Organization). Version 7.0.2 of the MINI will be used for this study. The results of these studies show that the MINI has similar reliability and validity properties, but can be administered in a much shorter period (mean 18.7 ± 11.6 min, median 15 min) than the above referenced instruments. It can be used by clinicians after a brief training session. At screening (Visit 1), subjects 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.
Massachusetts General Hospital-Antidepressant Treatment History Questionnaire (MGH-ATRQ)	The MGH-ATRQ is a self-rated scale used to determine treatment resistance in major depressive disorder. The scale examines the efficacy (improvement from 0%, not improved at all to 100% completely improved, and adequacy of a treatment. Subjects are asked by clinician about treatment adherence to each medication trial and examines the subjects' antidepressant history to identify pseudo-resistance and treatment resistance. The MGH-ATRQ will be collected at screening (Visit 1) only. This will be captured electronically.

McLean Screening Instrument for Borderline Personality Disorder	The MSI-BPD is a commonly used measure to assess for BPD. The scale consists of 10 items based on the DSM-5 BPD criteria; the first 8 items represent the first eight criteria in the DSM-5 for BPD diagnosis, while the last two questions assess the paranoia and dissociation criteria for BPD. Scores for the MSI-BPD range from 0 to 10, with each item rated as "1" if present and "0" if absent. A score of 7 or higher indicates a likelihood for the subject to meet criteria for BPD. The MSI-BPD will be collected at screening (Visit 1) only. This will be captured electronically.
Adult Self-Report Scale	The ASRS is a self-reported questionnaire used to determine the presence of attention-deficit/hyperactivity disorder in adults. The screener (6-item) version of the scale will be used in this study. The first question concerns inattention and the other 5 questions assess hyperactivity-impulsivity. Each question is answered on a 5-point Likert-type scale, ranging from "Never" to "Very Often". This scale will be obtained at Screening (Visit 1) only and will be captured electronically.
Scale to Assess Therapeutic Relationships – Patient and Clinician Version	The STAR-P and STAR-C is a 12-item measure assessing the therapeutic relationship between patient and clinician on three components: Collaboration, Positive Clinician Input, and Emotional Difficulties (clinician version)/Non-Supportive Clinician (patient version) input. The Collaboration subtest reflects a good rapport and a shared understanding of goals, mutual understanding, openness, and trust. Positive Clinician Input reflects the perception (by the subject) of the clinician to encourage, support, and listen to the subject. Emotional Difficulties/Non-Supportive Clinician Input reflect problems in the relationship. The range of total scores for both versions is 0–48, with a higher score suggesting better therapeutic relationships. Each version of the scale takes approximately 5 min to complete. Total scores and subscale totals can be obtained. The STAR-P and STAR-C will be collected at Baseline (Visit 2) only. These will be captured electronically.

Five Dimension Altered States of Consciousness Questionnaire	The 5D-ASC measures the acute drug effects using 5 primary dimensions and respective subdimensions to assess alterations in mood, perception, and experience of self in relation to environment and thought disorder. The 5 dimensions include *oceanic boundlessness*, *anxious ego dissolution*, *visionary restructuralization*, *auditory alterations*, and *reduction of vigilance*. This will be administered immediately after the psilocybin session on Day 0 (Visit 3). This will be captured electronically.
The Positive and Negative Affect Schedule	The PANAS measures the acute emotional drug effects, and comprises 2 mood scales that measure positive and negative affect. Subjects 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 effect. This will be administered at baseline (Visit 2), the day after the psilocybin session (Visit 4), and at week 3 (Visit 7). This will be captured electronically.
Emotional Breakthrough Inventory	The EBI is a VAS that describes the intensity and quality of the emotional experience following the psilocybin session, developed by the Imperial College London. This is collected on day 1 (Visit 4) electronically.
Mindstrong Application	If the subject opts to participate in the Mindstrong portion of the study, an app will be activated on the subject’s mobile phone at Visit 1; it will be deactivated at the EOS. Mobile data collection: The Mindstrong app will collect data from the subject’s smart phone and periodically send these data back to the Mindstrong secure database. The subject will not need to do anything to collect these, except use their phone as they normally do. The data collected from the subject’s phone will include: a) Number of and time of phone calls/e-mails/texts (content will not be collected); b) Location information from the GPS; c) Orientation of the smart phone (the way the phone is pointing); d) Acceleration of the smart phone (sudden movements of the phone); e) Keystroke information with characters redacted; and

	f) Gestures used (taps, swipes, other). The app may also maintain a list of target words and the subject's use-frequency of these words. These words will be completely stripped from their context, thus preventing the content of any particular message from being deciphered. The data collection application does NOT collect information on who or what number the subject calls or receive calls from. The data collection application does NOT capture the content of messages the subject sends or receives in a readable format. No personally identifiable information is captured and all other data are encrypted on the smartphone before transmission to the Mindstrong data enclave hosted on Amazon Web Service's cloud computers. Specifically, the application does NOT collect: a) Email addresses of the emails that the subject sends or receives; b) Phone numbers of the phone calls that the subject makes or receives; c) Phone numbers of the text messages that the subject makes or receives; and d) Messages sent or received in a readable format.

Subject Recruitment

A total of 216 subjects are planned to be enrolled in the study examining psilocybin treatment for treatment resistant depression.

Subjects meeting all the following inclusion criteria as shown in Table 4F below should be considered for admission into the study. No deviations will be permitted from the inclusion criteria.

Table 4F. Study Inclusion Criteria

No.	Criteria
1	Signed consent form
2	18 years of age or older at screening; (USA only) less than age 55 at screening.
3	At least moderate MDD (single or recurrent episode as informed by DSM-5; if single episode, duration of ≥ 3 months and ≤ 2 years) based on medical records, clinical assessment and documented completion of the version 7.0.2 MINI

4	HAM-D-17 (17-item) score ≥ 18 at screening (Visit 1) and at Baseline (Visit 2)
5	Failure to respond to an adequate dose and duration of 2, 3, or 4 pharmacological treatment 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.
6	McLean Screening Instrument for Borderline Personality Disorder < 7 at screening (Visit 1)
7	Have successfully discontinued all antidepressant medications at least 2 weeks prior to Baseline (Visit 2)
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

Subjects meeting any of the psychiatric or general medical exclusion criteria shown in Table 4G and Table 4H below will not be enrolled in the study. No deviations will be permitted from the exclusion criteria.

Table 4G. Psychiatric Exclusion Criteria

No.	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, or any serious psychiatric comorbidity as assessed by medical history and structured clinical interview (version 7.0.2 MINI).
2	Prior electroconvulsive therapy and/or ketamine for current episode
3	Current cognitive behavioral therapy (CBT) that will not remain stable for the duration of the study. CBT cannot be initiated within 21 days of Baseline.
4	Current (within the last year) alcohol or substance abuse as informed by DSM-5 at screening (Visit 1)
5	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 subject interview
6	Depression secondary to other medical conditions.

7	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.

Table 4H. General Medical Exclusion Criteria

No.	Exclusion Criteria
1	Women who are pregnant, nursing, or planning a pregnancy. Subjects 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 (Visit 1) and baseline (Visit 2)
2	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 [USA only] QTc > 450 msec) or clinically significant arrhythmia within 1 year of signing the ICF
3	Uncontrolled insulin-dependent diabetes.
4	Seizure disorder.
5	Positive urine drug screen for illicit drugs or drugs of abuse (USA only: to include but not limited to opiates, PCP, cocaine, amphetamines, methamphetamines, benzodiazepines, barbiturates and methadone; cannabis for medicinal purposes or recreational use is permitted) at Visit 1 and Visit 2. Any positive urine drug test will be reviewed with subjects to determine the pattern of use and eligibility will be determined at the investigator's discretion in conjunction with the MM.
6	Current enrolment in any investigational drug or device study or participation in such within 30 days of screening (Visit 1)
7	Current enrolment in an interventional study for depression or participation in such within 30 days of screening (Visit 1)
8	Abnormal and clinically significant results on the physical examination, vital signs, ECG, or laboratory tests at screening (Visit 1)
9	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 subject if he/she takes part in the study

All subjects will then be seen weekly for at least 3 weeks prior to the psilocybin session (Visit 3) to ensure the safe discontinuation of current antidepressant therapy required by the protocol. Rescreening of subjects considered not eligible for the study will be allowed.

Psilocybin Dose and Administration

Subjects will be randomized to the appropriate therapy after it is confirmed at baseline (Visit 2) that the subject remains eligible to participate in the study. Randomization will be stratified by country. Each subject will be assigned 1 treatment bottle containing 5 capsules packaged in a double-blind fashion, depending on the randomized treatment arm, the bottle will contain 1 of the following:

(a) 10-mg treatment bottle: 2 × 5-mg capsules and 3 × placebo capsules;

(b) 25-mg treatment bottle: 5 × 5-mg capsules; or

(c) 1-mg treatment bottle: 1 × 1-mg capsule and 4 × placebo capsules.

After a light breakfast taken 2 h prior to dosing and under observation of research personnel, 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 may be necessary to swallow the dose. Research personnel will ensure the entire 5-capsule dose has been swallowed.

To prepare for the drug experience, the subject will take the appropriate dose of psilocybin and lie down on a couch in a room with dim lights and a standard playlist of relaxing music playing quietly. A trained therapist will be present with the subject 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 subjects will be asked to remain in the room for the duration of the session regardless of the intensity of the effects, preferably 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 subject (i.e., ask how the subject is doing) in 30- to 60-min intervals post-dosing. A light meal and fruit will be available for the subject.

About 5 to 6 h after dosing, trained therapist will discuss the psilocybin experience with the subject. The subject is to be discharged 6 to 8 h post-dosing when, in the opinion of the investigator, the acute effects of psilocybin are resolved. The subject will 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 subject.

Psychotherapeutic Goals of Psilocybin:

The psychotherapeutic goals of the psilocybin session are to:

(a) Ensure psychological safety essential for optimal clinical efficacy;

(b) Allow subject's subjective experience to unfold naturally within the boundaries of the therapeutic intention set at the preparation;

(c) Maintain subject's attention and awareness on the experience of the present moment thus allowing exposure and processing of the challenging emotional states and personal memories; and

(d) Generation of insights and solutions for the resolution of challenging personal situations, conflicts and traumatic experiences.

Methods:

Psychotherapeutic methods of the psilocybin session have the following objectives:

(a) Psychological safety: effective management of anxiety is essential to safety, tolerability and efficacy of psilocybin;

(b) It has also been shown in previous studies that severe prolonged anxiety in the beginning of the experience could adversely affect the efficacy of psilocybin, therefore the management of anxiety during the onset of the session is an essential skill of psilocybin therapists. Anxiety during the onset of action is not uncommon, and the therapists are specially trained to recognize and actively manage subjects through such periods of anxiety until the subject is comfortable enough to continue on their own. The examples of such active guiding include:

(i) Remember you enrolled in this research study of psilocybin for treatment of your depression. As psilocybin takes effect, some anxiety and fear are expected. It is part of the process. Remember we practice relaxation and breathing experiences for situations like this?

(ii) Let's take deep breaths together and focus on the sensations of the breath throughout the body. As you do this, pay attention to the rhythm of your breath and watch it becoming deeper and slower. Let go of muscle tension with every exhalation.

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

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

In preparation for the psilocybin session, therapists demonstrate and practice skills of self-directed inquiry and experiential processing with subjects. Subjects are encouraged to face and explore their experience, including the challenging ones. During the peak and later stages of the session, self-directed inquiry and experiential processing become essential for subjects to develop a different perspective on their personal challenges and conflicts, and to generate their own solutions. Such self-generated insights are not only therapeutic because of the emotional

resolution, but also empowering to subjects. This approach is used in MDMA-assisted psychotherapy for treatment of PTSD and is particularly helpful in the event of emergent traumatic memories.

Structure of the Psilocybin Session:

The psilocybin session is supported by two appropriately qualified research personnel. The study psychiatrist will be in the immediate vicinity of the session to respond to any emergencies.

On the day of the session, subjects come in early in the morning with the goal to take the psilocybin treatment around 9 am.

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

The treatment rooms in all trial sites are furnished in soft furniture in muted colors to create a non-clinical calming feel. All treatment rooms are equipped with a high-resolution sound system that allows for simultaneous ambient and earphone listening.

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

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

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

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

therapeutic touch should be limited to hand and forearm areas only, or to the form of physical support that was agreed to during preparation.

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

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

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

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

(a) It is almost 6 o'clock. What do you normally do at this time of the day?

(b) What do you usually have for dinner?

(c) What do you like to cook?

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

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

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

Before the Session:

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

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

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

(a) Will stay in the room for the duration of the session;

(b) Will follow the therapist's instructions as all directions are given entirely to ensure their safety;

(c) Have an accurate mutual understanding of ways the therapist can provide support during the session, including interpersonal grounding, guided imagery and breathing exercises;

Key components of mental set/intention are also reviewed with the subject and include the following:

(a) Every experience is welcome; nothing to censor or avoid;

(b) Face anything that looks potentially frightening as rapidly and openly as possible;

(c) Reach out for grounding, support or sharing at any time;

(d) Remember key instructions: Trust, Let Go, Be Open;

(e) Remember to breathe deeply if needed;

(f) You'll never be left alone;

(g) No need to entertain the therapist/assistant; and

(h) This is your day. We're with you, whether you need us or not.

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

Before the drug's effects begin, it is helpful to re-establish the subject's stated goals for the treatment and to revisit the question: "What does feeling better or recovery feel like?" The subject is reminded that their primary task during this session is to simply collect new and interesting experiences which can then be discussed with the therapist during the integration

phase. The therapist can remind the subject of the purpose of the psilocybin therapy and the role of experiential processing, namely allowing the subject to be open and curious to whatever arises and encountering thoughts and feelings previously unknown to them. It should be emphasized that this process inherently requires letting go and a willing passivity to the psychedelic experience; the willingness to let go is correlated with better outcomes in psilocybin therapy. The therapist should remind the subject that the therapeutic team will be supporting them at all times.

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

Onset of Action:

Setting and Music

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

Managing Anxiety

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

During the acute onset of action, the subject might experience perceptual changes in visual, auditory or olfactory modes, and a range of unusual physical sensations. These

experiences could be anxiety-provoking, particularly in psychedelically naive subjects. During preparation, the therapist encourages the subject to become curious about these experiences and to freely explore them.

If the subject continues to manifest anxiety and emotional distress, the therapist may offer therapeutic touch or interpersonal grounding, if that is something the subject has agreed to during preparation and has been rehearsed. An example of interpersonal grounding would be: "I want to state again my commitment to be here for you. I will do whatever is necessary to make this a safe place for you so that you can fully experience whatever comes up. If what comes up is difficult, I'd like you to try and stay with it and explore it as much as you can. Please ask me for whatever you need."

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

The therapist encourages the subject to focus inwards and fully immerse him/herself in all aspects of the experience. The subject may want to practice guided imagery or breathing relaxation techniques in preparation.

Managing Distractions and Avoidance

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

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

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

And if the subject continues to engage in the conversation, the therapist can say: “Perhaps you can focus attention to the details so that we can talk about it later. If you talk about this now, you will be less able to focus on the experience and might miss important details.”

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

Sometimes a subject might ask to go to the bathroom or have a drink of water. The sudden and urgent character of such requests might suggest that they are really trying to avoid emerging material. In such cases, the therapist might suggest: “We will take a bathroom break at the end of this piece of music” or “I will get you water in a little while. Why don’t you put the eye shades back on and relax for a few minutes?”

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

Challenging Shifts Versus Adverse Events

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

Support can be in the form of therapeutic touch, verbal reassurance, guided imagery or a breathing exercise. It is advisable to apply one technique at a time to allow for minimal intervention and interference with the subject’s unique process. In the preparatory session, the therapist and subject may have discussed the most helpful ways to support in case of emotional distress. It might be useful to remind the subject about this conversation by stating: “You remember I told you that anxiety is to be expected and we have agreed that I may support you though physical grounding. If you feel anxious, please reach out for my hand or let me know what else might help you.” Another example of how to handle emotional distress in the subject is shown below:

Subject: “The negative feelings are getting really overwhelming now”

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

Subject: “Yeah. You suggested I should sit with them.”

Therapist: “How does that sound to you?”

Subject: “It’s going to be difficult, but I’ll try. If I can’t, can you help me?”

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

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

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

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

Therapist: "How do you feel about that?"

Subject: "It's difficult."

Therapist: "What's making it difficult?"

Subject: "I'm not sure."

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

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

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

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

Use of Rescue Medication:

If, in the judgement of the investigator, the subject cannot be calmed through all the available methods and is presenting a current threat to him/herself or others, then the use of benzodiazepines and/or antipsychotics is allowed. These should be administered according to their respective approved prescribing information and dose levels. The subject should be made safe in the least invasive and distressing way possible.

Peak Experience:

With adequate dosage and an acute onset of action, a 'peak' experience may occur about 60-90 minutes after ingestion. Factors that influence the quality and intensity of peak experiences include the subject's ability to stay with whatever arises in awareness, their ability to relax and let go of expectations and fears, dose of psilocybin, etc.

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

Subjects who reach peak non-dual experience tend to be quiet; even non-responsive. In the unlikely event that a subject would express a need to prematurely attempt to share such an experience, it should be viewed as distraction or avoidance. The therapist needs to encourage

the subject to stay quiet and focus on the sensations, insights and feelings, and to collect as many details about the experience as possible so as to be able to relate the story later. However, in true ego-loss and non-dual experiences, there is no ego present. When recalled in memory, subjects usually claim such states to be beyond language.

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

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

Conclusion of Psilocybin Session:

The drug effects last for 4-6 hours. During the final phase, it's important that the subject doesn't prematurely terminate the session by excessive talking. Even if little appears to be happening, periodic returns to the couch with music, headphones and eyeshade often provide for not only unexpected new experiential content, but safe and complete closure. The use of music is continued and light conversations between the therapist and subject are encouraged. This serves the dual role of re-orienting the subject to everyday reality and enabling the therapist to assess for immediate risks. By having a light casual conversation about dinner or the weather, the therapist assesses whether the subject is struggling to re-enter reality, or is distressed by the content of the session.

This can be discussed over a light meal with the subject, which — if they choose — can include the subject's family members. The therapist needs to be mindful that the subject is adequately reoriented to everyday reality, and be certain that the subject is fully competent to travel before making the journey home. If the subject requires a longer period of time to return to

normality, the therapist is expected to remain with the subject. If the subject requires emotional support due to a difficult session, the therapist is required to support the subject until the discomfort is resolved and the subject is fully back in everyday reality. The therapist should use open questions and empathic attention, as in previous sessions, to ensure that the subject feels supported.

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

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

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

When judged safe and functional, subjects are discharged in the care of a friend or a family member, referred to as a companion. This person is not the aforementioned caregiver who completes the EQ-5D-3L. Plans for the follow-up visit the next morning are confirmed prior to discharge.

Subjects who live more than 30 minutes away from the treatment center may be offered nearby accommodation in a hotel.

When the subject is ready to leave, he/she will be given information regarding the time and location of the next session (safety assessment and integration within 24 hours of the psilocybin session) as well as contact numbers if help is needed before then. The therapist is expected to be available 9am-5pm on weekdays and the emergency services number can be used on weekends and evenings. The subject must agree not to drive or use alcohol during the evening following the psilocybin session. The therapist should check in with the subject and family member(s) later in the evening to confirm that the subject is comfortable and safe.

Subjects who may have an unusually prolonged experience or remain in severe distress and are considered at risk for adverse reactions will be asked to stay for observation overnight and will be supported by research personnel.

In case of psychotic reaction, subjects will be assessed by a study psychiatrist and hospitalized as needed. The emergency protocol specifies oral benzodiazepines, followed by antipsychotics as needed.

Concomitant Therapy:

All prescription and non-prescription medications (e.g., over-the-counter drugs and herbal supplements) that subjects report taking during the 30 days prior to screening (Visit 1) 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 informed consent form was signed through the end of study participation.

Changes, additions, or discontinuations to medications will be assessed and recorded during each study visit. All as-needed prescriptions should be converted to reflect actual number of pills or dose taken per day.

Medications for the management of concurrent anxiety and insomnia, or non-psychiatric medications that have a potential psychotropic effect are permitted within the following limitations. From the initial screening (Visit 1) through final study visit (Visit 10, EOS), subjects 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 (e.g., pseudoephedrine for allergies or cold symptoms; zopiclone for sleep disorders) should be used no more than 2 times a week and not in the 12 h before any study assessment. Documentation of the use of adjunctive anxiolytics, hypnotics, or medication with potential psychotropic properties (including over-the-counter preparations) will be obtained at each clinic visit.

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

In some embodiments, the following plan should be followed to manage the occurrence of physiological adverse events during the psilocybin session:

(a) Headaches - Tylenol 650 mg taken by mouth, once a day;

(b) Symptomatic elevated blood pressure - short-acting beta blocker on the formulary once a day by mouth or IV;

(c) Chest pain - ECG, nitroglycerin sublingual, acetylsalicylic acid once a day and further evaluation as needed;

(d) Nausea, Vomiting, Aspiration - precautions, ice chips.

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

Benzodiazepine anxiolytics is the pharmacological intervention of choice in case of acute psychological distress (e.g., medications such as lorazepam or alprazolam that have a rapid onset, a short time until peak plasma concentration, and a short duration of therapeutic action; the oral route is preferable because IV injection procedures may further exacerbate the subject's anxiety).

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

In case of development of acute anxiety or psychotic symptoms requiring pharmacological intervention, the subject will be managed appropriately. Rescue medication should be administered according to their respective approved prescribing information and dose levels. The subject may be discharged from the clinic when, in the opinion of investigator, the condition has stabilized. The subject will be accompanied home. The site is to be notified by the subject that they have returned home safely, and in the absence of receiving a phone call site staff will directly contact the subject.

Adverse Events

Throughout the course of the study, all adverse events (AEs) will be monitored and recorded and will include the AE's description, start and end date, seriousness, severity, action taken, and relationship to the treatment. If AEs occur, the first concern will be the safety of the study subjects.

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable 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.

Efficacy and Outcome Measures:

Efficacy and outcome measures include MADRS, QIDS-SR-16, SDS, GAD-7, DSST, EQ-5D-3L (subject and caregiver), and WSAS.

The change from baseline in MADRS total score at week 3 will be evaluated with a mixed effects model for repeated measures analysis. The model will include treatment, visit, study site, prior psychedelic experience, treatment by visit interaction, subject as a random effect, and baseline MADRS total score. Comparison of the psilocybin optimal dose versus 1 mg psilocybin will be performed at the 0.05 testing level. A sensitivity analysis will be performed on the primary mixed model repeated measures model adding treatment by study site or country interaction into the model. If it is significant (at the 10% level), then further investigations of sites will be performed.

Four additional efficacy endpoints that are dichotomous variables (proportion of subjects who are responders, remitters, and sustained responders) will be analyzed using the Cochran Mantel Haenszel chi square test, stratified by country, to compare the psilocybin optimal therapeutic dose versus 1 mg psilocybin. A stepdown procedure to correct for multiplicity will be employed.

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

Response and remission rates will be summarized at each visit.

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

Scores for all efficacy endpoints, including dimension scores of the EQ-5D-3L and the EQ VAS, will be summarized over time using descriptive statistics for all visits during the observation period.

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

Continuous behavior sampling will be tested with the Mindstrong application technology in a subgroup of smart phone users consented to this part of the study. Subjects who do not consent to the app installation, or don't have a smart phone, will not be excluded from the study. Following the installation of the Mindstrong app on the subject's smart phone, the app will begin to collect data from the smart phone and periodically send these data back to the secure database. The subject does not need to do anything at this stage, except use their phone as they normally do. As explained above, personal data from mobile phone usage will be analyzed in a sub-group of consenting subjects.

The correlation between sensor data, keyboard behavior, or voice and speech metrics will be assessed for correlation with standard clinical assessments and the ability of app features to identify impending relapse before clinical change is apparent with traditional ratings. The goal of these exploratory assessments is to identify mobile use patterns (app features) predictive of clinically significant mood changes that will have an impact on care and treatment outcomes.

Analysis of Safety:

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

Columbia-Suicide Severity Rating Scale (C-SSRS)

Item scores from the C-SSRS, all visits by randomized treatment, the item scores from the version assessing suicidality since the last visit, and all postbaseline visits (Visit 3 to Visit 10, inclusive) by treatment will be tabulated. Summary statistics of suicidal ideation and suicidal behavior following psilocybin administration will be presented by randomized treatment.

Adverse Events

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

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

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

Electrocardiographic Data

The ECG data will be summarized descriptively based on measures of change in each ECG parameter from Visit 1 to post-treatment (Visit 4). Frequency tabulations of the abnormalities will be provided. ECG variables to be analyzed 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.

Laboratory Data

Laboratory data (hematology 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 subjects with normal/abnormal values at Baseline versus post-treatment. The frequency of laboratory abnormalities will be tabulated. By-subject data listings will flag laboratory values that are outside normal reference ranges or markedly abnormal findings.

Vital Signs

Changes from baseline in vital signs, blood pressure (systolic and diastolic), body temperature, pulse rate, and respiratory rate, will be summarized for each treatment group using descriptive statistics. The last measurement obtained prior to treatment administration will serve as baseline. The percentage of subjects with values outside clinically important limits will be summarized. A listing of weight and height at Visit 1 will be provided.

Demographic and Baseline Characteristics

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

Example 6. Clinical Study Examining Psilocybin for the Treatment of Bipolar Disorder

Study Rationale

Bipolar depression remains the mood disorder condition with the fewest somatic treatment options. Current FDA approvals for bipolar depression are limited to several atypical antipsychotics and one anticonvulsant. Subjects with a history of bipolar type I (BP I) versus bipolar type II (BP II) often get lumped into one treatment category, while evidence suggests different treatment paradigms should be used. A recent study showed that BP II patients may do just as well with or without mood stabilizers.

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. Given the effectiveness of psilocybin in a difficult to treat unipolar depressed group, there is an open question as to whether this effect may carry over to subjects with bipolar disorder that includes a history of hypomania or low grade mixed states.

This study assesses the effect and efficacy of 25 mg of psilocybin in subjects with treatment-resistant type 2 bipolar depression. This study is configured to determine if there is a

signal for response as well as sufficient safety for the use of psilocybin in depressed patients who meet the diagnostic criteria for BIP III.

Study Objectives

Two objectives of this study are to:

(a) determine the effect of psilocybin at 25 mg; and

(b) demonstrate efficacy of 25 mg of psilocybin under supportive conditions to adult subjects with BP II, current episode depressed, in improving depressive symptoms. Depression symptoms will be assessed by the change in the Montgomery-Asberg Depression Rating Scale (MADRS). Baseline is defined as the assessment score obtained on day -1. The primary time point is week 3; however, this variable will be analyzed for the change from baseline to day 1 and weeks 6, 9 and 12.

Additional objectives of this study are to:

(a) assess the efficacy of psilocybin in the: (i) proportion of participants with response defined as >50% decrease in MADRS total score from baseline to week 3. This will also be assessed at day 1 and at weeks 1, 6, 9, and 12; (ii) proportion of participants in remission defined as the participants with a MADRS total score <10 at week 3. This will also be assessed at day 1 and at weeks 1, 6, 9, and 12; and (iii) proportion of responding participants who sustained a response up to week 12 defined as those with >50% decrease in MADRS total score on or before week 6 and remaining at week 12; and

(b) evaluate the safety and tolerability of psilocybin in participants with BP-II, current episode depressed, based on tracking treatment emergent mania or hypomania as assessed by the Young Mania Rating Scale (YMRS), adverse events (AEs), changes in vital signs, and suicidal ideation/behaviour score at all visits. The suicidal ideation/behaviour score will be measured using the Columbia-Suicide Severity Rating Scale [C-SSRS].

The exploratory objectives of this study are to evaluate the effects of psilocybin on quality of life and wellbeing, functioning and associated disability, cognitive function, and anxiety. A description of exploratory objectives is shown in Table 5A below.

Table 5A. Exploratory Objectives

Assessment	Description	Time of Assessment
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF)	Level of life satisfaction and enjoyment	Scale score change from baseline to week 3 and week 12
Sheehan Disability Scale (SDS)	Functioning and associated disability	Scale score change from baseline to week 3 and week 12

Generalized Anxiety Disorder 7 (GAD-7)	Level of anxiety	Scale score change from baseline to week 3 and week 12
Quick Inventory of Depressive Symptomatology Self Rated (QIDS-SR-16)	Level of depression	Scale score change from baseline to day 1 and weeks 1, 2, 3, 6, 9, and 12
Work and Social Adjustment Scale	Psychological functions and predictor of response durability	Scale score change from baseline to week 3 and week 12
Positive and Negative Affect Schedule	Correlation with primary and secondary outcomes as possible predictors of response	
Five Dimension Altered States of Consciousness Questionnaire	Correlation with primary and secondary outcomes as possible predictors of response	Immediately following the psilocybin session on Day 0
Scale to Assess Therapeutic Relationship	Correlation with primary and secondary outcomes as possible predictors of response	

Study Endpoints

One endpoint is the change in MADRS total score from baseline (Visit 2) to 3 weeks (Visit 7) from day 0 (Visit 3). The primary efficacy endpoint will be evaluated with a mixed-effects model for repeated measures.

Additional endpoints are:

(a) the proportion of participants with a response (defined as a >50% improvement in MADRS total score from Baseline) at week 3 post-psilocybin;

(b) the proportion of participants with remission (defined as a MADRS total score ≤10) at week 3 post-psilocybin;

(c) the proportion of participants who have a sustained response at week 12; and

(d) time to event measures include restart antidepressant medication for any reason, restart medication for continuing depressive symptoms, and relapse from a previously recovered state (clinical judgement, supported by the QIDS-SR-16). Subjects who withdraw from the study will be censored from the time to event analysis.

The exploratory endpoints are the change from baseline in Q-LES-Q-SF, SDS, GAD-7, QIDS-SR-16, and WSAS at week 3.

Methods

This is an exploratory open-label study in which the study population will receive one dose of psilocybin. This population will be used for all summaries of subject accountability, demographic and baseline data, and safety information, including AE incidence.

The study will take place over a 12 week period where the subject will undergo screening (Visit 1), baseline assessment (Visit 2), psilocybin administration (Visit 3), and a series of follow-up visits (Visits 4-10) to assess the effects of psilocybin on bipolar disorder. A timeline of the study design is shown in Fig. 12.

Subjects:

The majority of subjects will have no prior exposure to psilocybin or "magic mushrooms". If the subject has past exposure to psilocybin it has to be more than 12 months prior to screening and is not during the current depressive episode.

Subjects meeting all the following inclusion criteria as shown in Table 5B below should be considered for admission into the study.

Table 5B. Study Inclusion Criteria

No.	Criteria
1	Signed consent form
2	Age between 18 and 65 at screening (Visit 1)
3	Must meet DSM-5 criteria for BP II episode based on medical records, clinical assessment, and documented completion of the version 7.02 MINI
4	HAM-D-17 (17-item) score ≥ 18 at screening (Visit 1) and at baseline (Visit 2)
5	YMRS ≤ 10 at Visit 1 and Visit 2
6	Failure to respond to an adequate dose and duration of 2 or more pharmacological treatments for the current episode as determined through the MGH-ATRQ. The current episode is greater than 3 months but less than 2 years. Failure includes inadequate response to an adequate duration and dose or failure to reach an adequate dose and duration due to intolerance. Augmentation with an add on treatment counts as a second treatment.
7	Have successfully discontinued all serotonergic medications at least 2 weeks prior to baseline (Visit 2)

8	Ability to complete all protocol required assessment tools without any assistance, and to comply with all study visits

The subject's medical history regarding present and previous diseases, medication, and allergies will be gathered for the purpose of evaluating potential participation in the study as well as interpretation of study results.

Subjects meeting any of the psychiatric or general medical exclusion criteria shown in Table 5C and Table 5D below will not be enrolled in the study.

Table 5C. Psychiatric Exclusion Criteria

No.	Exclusion Criteria
1	Current/history of bipolar I disorder, schizophrenia, psychotic disorder (including substance induced or due to a medical condition), delusional disorders, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder, as assessed by medical history and a structured clinical interview (version 7.02 MINI)
2	Current cognitive behavioral therapy (CBT) that will not remain stable for the duration of the study.
3	Current (or < 1year remission) alcohol or drug abuse as defined by DSM-5 at screening (Visit 1).
4	Significant risk of suicide based on the C-SSRS defined as answering "YES" to question 4 or 5 for "Suicidal Ideation" [past 1 month] on the Columbia-Suicide Severity Rating Scale, and/or answering "YES" to any question for "Suicidal Behavior" [past 3 months] on the Columbia-Suicide Severity Rating Scale). Or, if active suicidal activity or ideation during the current episode, eligibility will be determined at the investigator's discretion.
5	Depression determined to be secondary to other severe medical conditions.
6	Other conditions, personal circumstances and behavior judged to be incompatible with establishment of rapport or safe exposure to psilocybin.

Table 5D. General Medical Exclusion Criteria

No.	Exclusion Criteria
1	Women who are pregnant, nursing, or planning a pregnancy
2	Cardiovascular conditions: recent stroke, recent myocardial infarction, hypertension or clinically significant arrhythmia within 1 year of signing the ICF

3	Untreated or uncontrolled insulin-dependent diabetes
4	Seizure disorder
5	Positive urine drug screen for illicit drugs or drugs of abuse

Visit 1: Screening Procedure

Subjects will be assessed for their eligibility according to the inclusion and exclusion criteria shown in Tables 5C-5D before study inclusion.

Subjects will be screened for eligibility using the Mini International Neuropsychiatric Interview (MINI) screening tool and the Hamilton Depression Rating Scale (HAM-D-17), the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ), the Young Mania Rating Scale (YMRS) and the Columbia-Suicide Severity Rating Scale (C-SSRS). The subject will also be evaluated with the QIDS-SR-16. YMRS is a clinical interview scale used to assess the severity of manic states in individuals with mania. A description of the other assessments used in the screening procedure are described in Example 6, Tables 4C-E.

The subject will also undergo a medical history examination, an electrocardiogram (ECG), blood test and obtainment of vital signs. The blood sample will determine hematology, standard biochemistry variables and relevant biomarkers. We will also reguire urine samples for specific biochemistry variables, for illicit drugs and for women of childbearing potential in the form of a pregnancy test. A description of the medical assessments performed prior to psilocybin administration are described in Example 4, Visit 1 (screening).

Subjects will be informed not use any other prophylactic medication during the 2 weeks wash-out and the 12 weeks study period.

Visit 2: Baseline (Day -1)

The baseline visit should occur the day before the anticipated psilocybin session. The MADRS assessment will be performed during the baseline visit as well as the assessments shown in Table 5A above.

Visit 3: Psilocybin Administration

The psilocybin administration session (Fig. 12, Day 0) will last approximately 6 hours and will be supported by a trained therapist.

The dosing session will take place in a purpose-built clinical research facility with extensive nursing and emergency support (e.g., Invicro). Efforts will be made to arrange the intervention room to promote relaxation without compromising medical safety. Mobile phones will be switched off during every session and efforts will be made to minimize unexpected interruptions.

All sessions will be supervised by at least two individuals. A study medical doctor will administer the active psilocybin (25 mg, 5 capsules of 5 mg) and be available on site during the dosing sessions. All capsules will be administered at the beginning of the session. If required, the medical doctor can attend the therapy room within less than 5 minutes.

Based on previous clinical studies with psilocybin, research personnel will not initiate conversation with the subject. However, research personnel will respond to the subject if they initiate contact. It is advised that active intervention is kept to a minimum during the acute experience. The subject is encouraged to explore their own mental space. Simple guided imagery or breathing exercises may be used to assist relaxation.

Guidelines on conducting clinical trials with psilocybin state that almost all cases of anxiety or nervousness may be handled by interpersonal support. However, diazepam will be available for treating any strong anxiety or panic reactions that is not abated by interpersonal support. The diazepam dose is the dose as suggested on pro.medicin.dk: 5 mg perorally, intravenously, or intramuscularly, 1-3 times per day.

After approximately 5 hours post-dose, most of the acute subjective effects of psilocybin will have subsided and the subject will undergo a thorough debriefing. This will involve encouraging the subject to give a detailed descriptive account of the experience. Dosing sessions will be video and/or audio recorded. Post-session interviews will also be video and audio recorded for qualitative analyses.

Subjects will be evaluated for safety and discharged home with a chaperone. Subjects will be advised to not operate an automobile, motorcycle or other motorized equipment for the rest of the day after psilocybin administration.

Visits 4-10: Assessments Following Psilocybin Administration

The day following psilocybin administration (Fig. 12, Day 1, Visit 4), subjects will be seen in person for a safety check, assessment of suicidality, and to discuss their experience during the psilocybin session. Safety will be evaluated by an ECG, blood test including liver function tests, vital signs, suicide risk as assessed by the C-SSRS, AEs and Serious AEs and YMRS. Subjects are allowed to share insights that may arise during psilocybin experience.

All subjects will be asked to remain off their antidepressant medications for at least 3 weeks following the psilocybin session until the primary endpoint assessment, or longer. Subjects who restart their antidepressant medications during the first 3 weeks after psilocybin administration will be assessed for reasons of resuming their medications and followed until 12 weeks post-psilocybin administration.

The primary endpoint is the change in MADRS total score from baseline (day -1) to 3 weeks from day 0. The primary efficacy endpoint (change from Baseline in MADRS total score at 3 weeks (Visit 7) from day 0 (Visit 3) will be evaluated with a mixed-effects model for repeated measures.

Risks, side-effects and discomfort

The side effects of psilocybin are dose-dependent and the dose administered in this study is about 2-3 times less than what is typically administered when psychedelic effects are desired. We expect that effects will only manifest to a limited degree, and we expect neither any considerable distress nor serious adverse reactions to psilocybin.

Subjects experiencing side effects from psilocybin treatment will be evaluated to determine whether the effect was expected or unexpected based on previously published human studies and the medical product dossier for psilocybin. Some of the expected side effects of psilocybin are considered unpleasant. However, we expect that the unpleasant effects will not be of significant nuisance to the subject. Further, we believe the risk of serious adverse reactions is extremely low under the circumstances in which psilocybin will be administered.

Subjects experiencing adverse events or reactions will be monitored, relevant clinical and/or laboratory evaluations will be performed, and treatment initiated. The severity of adverse events (e.g., adverse event, adverse reaction, serious adverse event and unexpected adverse reaction) are categorized and defined in Example 5.

Subjects may experience an increase in attack frequency throughout the course of the study because they must abstain from normal preventive medication.

Acute effects of psilocybin may include: visual disturbances (e.g. more vivid colors, apparent motion of surfaces), delusions, hallucinations, loss of attention to external stimuli, altered sense of time and space, auditory perceptual alterations, stimulation of mood and effect (e.g., euphoria, dysphoria), altered understanding of real events, spiritual/mystical/transcendental experiences, depersonalization, derealization and transitivism. Unpleasant effects are more common in higher dose-ranges such as 25mg and may include irritability, restlessness, anxiety, and anxiety reactions, and “bad trips” that may include bizarre or frightening images, paranoia, and complete derealization. Other transitory acute effects include: dizziness, nausea, gastrointestinal upset, muscle weakness and/or pain, shivers, tremors, mydriasis, hypertension, and tachycardia.

Blood samples are drawn either from venous punctures (butterfly needle) or from a temporary intravenous access in the antecubital vein (“venflon”). Slight discomfort is associated

with this, and there is risk of a subsequent non-clinically relevant hematoma. There is a very small risk of thrombophlebitis and infection associated with these procedures.

Example 7: Effect of Psilocybin on Sleep-Wake Disorders

To determine whether psilocybin may treat sleep-wake disorders, various doses of psilocybin were tested in an animal model to determine if psilocybin had an effect on wakefulness, non-rapid eye movement (NREM) and/or rapid eye movement (REM) sleep, as well as on common electroencephalogram (EEG) frequency bands.

Wistar-Kyoto (WKY) rats exhibit abnormal behavioural, hormonal, neurochemical as well as sleep-wake characteristics that are often associated with depression. Since WKY rats show decreased sensitivity to conventional monoamine-based antidepressant treatment, they are used as a model of TRD. WKY rats are known to exhibit enhanced REM sleep, a common feature in depressed patients.

Male (WKY) rats (200-250g) were implanted with electroencephalography (EEG) and electromyography (EMG) electrodes and telemetry transmitters under general anesthesia (2-5% isoflurane in Oxygen). A telemetry transmitter (HD-S02, Data Sciences International) was placed in the peritoneal cavity, and the wires of the transmitter were passed through the muscle wall and then sub-dermally to the scalp to act as EEG/EMG electrodes. Two bore holes were made in the skull (Fronto-parietal coordinates; Bregma +2mm anterior, midline +1.0mm lateral and Lambda 0mm, +1.5mm lateral). The positive EEG electrode was attached to the anterior bore hole and the negative EEG electrode to the posterior bore hole. Both electrodes were secured in place using a suitable adhesive agent (Cyanoacrylate gel, RS components). A second set of electrodes were sutured into the nuchal muscle to act as EMG electrodes. During the post-surgical recovery period (minimum 7 days), the rats received standard post-operative care and no experimental procedures were performed until the pre-operative body weight was regained.

The animals were not drug-naive at the beginning of the study as they were used in a previous study. The length of the washout period between the two studies was more than 3 months.

Animals were maintained on a 12/12 hour light dark cycle. On study days, the animals were placed in recording boxes and EEG/EMG, locomotor activity, as well as body temperature were recorded for 0.5 hours before and 24 hours after each dosing. All animals were dosed with saline vehicle first, followed by one of the drug treatments 24 hours later. Drug treatments included ketamine (5 and 10 mg/kg) administered subcutaneously (s.c.)) and psilocybin (1, 3 and 10 mg/kg); administered intraperitoneally (i.p.)).

All treatments were administered 2 hours after light onset. All animals received all treatment conditions by escalating the doses on a weekly basis, with a 6 day washout period between drug treatment and the subsequent vehicle treatment.

EEG, EMG, locomotor activity and body temperature data were acquired for 0.5 hours before and 24 hours after each treatment with Spike2 software (CED, Cambridge UK). EEG/EMG signals were amplified, analogue filtered (0.5-1 00 Hz), digitized (256 Hz), and then digitally filtered (EEG: 0.5-100 Hz and EMG: 5-100 Hz).

The subsequent EEG/EMG recordings were automatically scored as wake, non-REM (NREM) sleep, or REM sleep in 10 second epochs using SleepSign (Kissei Comtec, Japan).

Power spectral analysis was performed on EEG data recorded over the 0-1 hour, 1-7 hour and 11-19 hour periods post-treatment. EEG power spectra were computed for consecutive 2 second epochs by fast Fourier transformation (Hanning window, 0.5 Hz resolution) between 0.5-100 Hz. Epochs with artefacts (5xSTD of RMS) were discarded. Data were presented in 1 Hz bins, and the bins were marked by their upper limits.

Statistical analysis: Repeated measures ANOVA followed by Dunnett post-test was used to compare the different treatment groups (GraphPad, Prism 8).

In this study, both psilocybin (1, 3 and 10 mg/kg, i.p.) and ketamine (5 and 10 mg/kg) decreased the amount of REM sleep in a dose-dependent manner (Fig. 13A and 13B).

Psilocybin also caused a dose-dependent increase in wake amount and a slight decrease in NREM sleep amount during the light period (Fig. 13A and 13B). This was followed by a slight but significant increase in the amount of NREM sleep at the expense of wakefulness in psilocybin-treated rats during the dark period most likely caused by a rebound effect (Fig. 13A and 13C).

Psilocybin suppressed high-frequency gamma (30-100 Hz) oscillations in the EEG of WKY rats in the 1st hour post-treatment (Fig. 13D). In the subsequent part of the light period, psilocybin (1, 3 and 10 mg/kg, i.p.) increased both EEG theta (4-10 Hz) and beta (10-30 Hz) oscillations and suppressed EEG gamma oscillations in WKY rats (Fig. 13E).

Example 8: Co-administration of psilocybin and a benzodiazepine

The following example provides details of a study to determine the effects of low and high dose of the benzodiazepine alprazolam on the acute psilocybin experience in healthy volunteers, and to provide an evidence base for the use of benzodiazepines to control anxiety, which may be used to inform future dose and drug selection. This study also seeks to show the dimension of the psychedelic experience affected by GABAergic manipulation, including subjective (H D-

ASC) and neurological (fMRA), to help develop an understanding of which aspects are important therapeutically.

In a first dosing session, at t = 0; 315 µg/kg psilocybin (PSI) will be administered to a healthy, psychedelic naive patient (i.e., the patient has no prior experience taking psychedelic drugs). Approximately 4 weeks later, the patient will participate in a second dosing session. In the second dosing session, 315 pg/kg psilocybin will be co-administered to the patient with either (a) a placebo (PSI + PLA), (2) 0.25 mg alprazolam (PSI + 0.25 mg), or (3) 1 mg alprazolam (PSI + 1 mg) at t = 0.

In both dosing sessions, after the patient begins to have a psychedelic experience, the patient will be asked to provide a subjective rating approximately every 20 minutes of his or her experience intensity, blissfulness, and anxiety. Physiological measures of sympathetic simulation will be measured at t = 2-3 hours. At t = 7 hours, 11D-ASC (11-Dimension Altered States of Consciousness), PANAS (Positive and Negative Affect Schedule), EDI (Ego-Dissolution Inventory) & blood cortisol will be evaluated. Longer term effects on wellbeing will also be evaluated after the psychological experience has ended.

Functional mMRI (fMRI) will also be used to measure the effects of low and high dose alprazolam in these patients. Individuals in each group (PSI + PLA, PSA+0.25 mg, PSI + 1mg) will be randomized for resting state fMRI scanning at the peak of the experience. Brain regions associated with fear, panic, and anxiety will be examined. The following comparisons will be performed: (PSI + PLA) vs (PSI + 0.25) mg vs (PSI + 1mg). It is hypothesized that activation in fear regions will decrease disproportionately to other neural correlates of the psychedelic state.

Example 9: Co-administration of psilocybin and a benzodiazepine

The following examples 9A and 9B provide details of studies that will be used to determine the effects of low and high dose benzodiazepine (e.g., alprazolam or diazepam) on the acute psilocybin experience in healthy volunteers. The purpose of these studies is to provide an evidence base for the use of benzodiazepines to control psychedelic anxiety, which may be used to inform future dose and drug selection. This study also seeks to show the dimension of the psychedelic experience affected by GABAergic manipulation, including subjective (11D-ASC) and neurological (fMRI), to help develop an understanding of which aspects are important therapeutically.

Example 9A: Alprazolam

In a first dosing session, at t = 0: 315 µg/kg psilocybin (PSI) will be administered to a healthy, psychedelic naive patient (i.e., the patient has no prior experience taking psychedelic drugs) in an open-label manner.

Approximately 4 weeks later, the patient will participate in a second dosing session. In the second dosing session, 315 µg/kg psilocybin will be co-administered to the patient with either (a) a placebo (PSI + PLA), (2) 0.25 mg alprazolam (PSI + 0.25 mg), or (3) 1 mg alprazolam (PSI + 1 mg) at t = 0.

In both dosing sessions, after the patient begins to have a psychedelic experience, the patient will be asked to provide a subjective rating approximately every 20 minutes of his or her experience intensity, blissfulness, and anxiety. Physiological measures of sympathetic simulation will be measured at t = 2-3 hours. At t = 7 hours, 11D-ASC (11-Dimension Altered States of Consciousness), PANAS (Positive and Negative Affect Schedule), EDI (Ego-Dissolution Inventory) and blood cortisol will be evaluated. Longer term effects on well being will also be evaluated after the psychological experience has ended.

Functional mMRI (fMRI) will also be used to measure the effects of low and high dose alprazolam in these patients. Individuals in each group (PSI + PLA, PSA + 0.25 mg, PSI + 1mg) will be randomized for resting state fMRI scanning at the peak of the experience. Brain regions associated with fear, panic, and anxiety will be examined. The following comparisons will be performed: (PSI + PLA) vs (PSI + 0.25) mg vs (PSI + 1mg). It is hypothesized that activation in fear regions will decrease disproportionately to other neural correlates of the psychedelic state due to co-administration of alprazolam.

Example 9B: Diazepam

In a first dosing session, at t = 0: 25 mg psilocybin (PSI) will be administered to a healthy, psychedelic naive patient in an open-label manner.

Approximately 4 weeks later, the patient will participate in a second dosing session. In the second dosing session, 25 mg psilocybin will be administered to the patient. Additionally, the patient will also be administered (a) a placebo (PSI + PLA), (2) 2 mg diazepam (PSI + 2 mg), (3) 5 mg diazepam (PSI + 5 mg), (4) or 10 mg diazepam (PSI + 10 mg) at the same time as the psilocybin or at the peak of the psychedelic experience.

In both dosing sessions, after the patient begins to have a psychedelic experience, the patient will be asked to provide a subjective rating approximately every 15 minutes of his or her experience intensity, blissfulness, and anxiety. Heart rate, blood pressure and galvanic skin reaction will also be measured. After each session, 5D-ADC, PANAS, and blood cortisol will be

measured. Additionally, a standardized interview will be performed, to discuss the quality of the experience and to get any comments that may be overlooked in the surveys.

Physiological measures of sympathetic simulation will be measured at t = 2-3 hours. At t = 7 hours, 11D-ASC (11-Dimension Altered States of Consciousness), PANAS (Positive and Negative Affect Schedule), EDI (Ego-Dissolution Inventory) & blood cortisol will be evaluated. Longer term effects on wellbeing will also be evaluated after the psychological experience has ended.

Functional mMRI (fMRI) will also be used to measure the effects of low and high dose diazepam in these patients. Individuals in each group (PSI + PLA, PSA + 2 mg, PSI + 5 mg, PSI + 10 mg) will be randomized for resting state fMRI scanning at the peak of the experience. Brain regions associated with fear, panic, and anxiety will be examined. The following comparisons will be performed: (PSI + PLA) vs (PSI + 2 mg) vs (PSI + 5 mg) vs. (PSI + 10 mg). It is hypothesized that activation in fear regions will decrease disproportionately to other neural correlates of the psychedelic state due to co-administration of diazepam.

Example 10: Effect of alprazolam on 5-HT$_{2A}$ receptor binding by psilocybin

The following example provides details of a study used to determine whether alprazolam-induced changes in subjective experience during psilocybin therapy are due to changes in 5-HT$_{2A}$ occupancy. If not, downstream molecular and cellular effects that may be important in psilocybin's therapeutic effects may be preserved after co-treatment with a benzodiazepine.

In this study, [^{11}C]CIMBI-36 (a selective 5-HT2A receptor agonist positron emission tomography (PET) radioligand) will be used to investigate whether 5-HT2A binding is affected by placebo vs. alprazolam.

At time t=0, patients will be administered 25 mg psilocybin (PSI) in combination with either a placebo, or alprazolam. At t = 2 hours, patients will be given a tracer dose of [^{11}C]CIMBI-36. At t = 2-3 hours, a PET scan will be performed, to determine whether 5-HT2A binding is affected by either dose of alprazolam.

This study may optionally be performed using diazepam instead of alprazolam.

Example 11: Co-administration of psilocybin and a 5-HT$_{2A}$ specific antagonist

The following example provides details of a study used to determine the effects of low and high dose of ketanserin, a 5-HT$_{2A}$ specific antagonist on the acute psilocybin experience in healthy volunteers. The purpose of this study is to provide an evidence base for the use of 5-HT$_{2A}$ specific antagonists to control the negative side effects associated with a traumatic psychedelic experience, which may be used to inform future dose and drug selection. This study also seeks

to show the dimension of the psychedelic experience affected by GABAergic manipulation, including subjective (11D-ASC) and neurological (fMRI), to help develop an understanding of which aspects are important therapeutically.

In a first dosing session, at t = 0: 315 µg/kg psilocybin (PSI) will be administered to a healthy, psychedelic naive patient (i.e., the patient has no prior experience taking psychedelic drugs). Approximately 4 weeks later, the patient will participate in a second dosing session. In the second dosing session, 315 pg/kg psilocybin will be co-administered to the patient with either (1) a placebo (PSI + PLA), (2) low dose ketanserin (PSI + LD), or (3) high dose ketanserin (PSI + HD) at t = 0.

In both dosing sessions, after the patient begins to have a psychedelic experience, the patient will be asked to provide a subjective rating approximately every 20 minutes of his or her experience intensity, blissfulness, and anxiety. Physiological measures of sympathetic simulation will be measured at t = 2-3 hours. At t = 7 hours, 11D-ASC (11-Dimension Altered States of Consciousness), PANAS (Positive and Negative Affect Schedule), EDI (Ego-Dissolution Inventory) & blood cortisol will be evaluated. Longer term effects on well being will also be evaluated after the psychological experience has ended.

Functional mMRI (fMRI) will also be used to measure the effects of low and high dose ketanserin in these patients. Individuals in each group (PSI + PLA, PSA+LD, PSI + HD) will be randomized for resting state fMRI scanning at the peak of the experience. Brain regions associated with fear, panic, and anxiety will be examined. The following comparisons will be performed: (PSI + PLA) vs (PSI + LD) vs (PSI + HD). It is hypothesized that activation in fear regions will decrease disproportionately to other neural correlates of the psychedelic state due to co-administration of ketanserin.

Example 12: Co-administration of psilocybin and a 5-HT$_{2A}$ inverse agonist

The following example provides details of a study used to determine the effects of low and high dose of pimavanserin, a 5-HT$_2$A inverse agonist on the acute psilocybin experience in healthy volunteers. The purpose of this study is to provide an evidence base for the use of 5-HT$_2$A inverse agonists to control the negative side effects associated with a traumatic psychedelic experience, which may be used to inform future dose and drug selection. This study also seeks to show the dimension of the psychedelic experience affected by GABAergic manipulation, including subjective (11D-ASC) and neurological (fMRIA), to help develop an understanding of which aspects are important therapeutically.

In a first dosing session, at t = 0, 315 pg/kg psilocybin (PSI) will be administered to a healthy, psychedelic naive patient (i.e., the patient has no prior experience taking psychedelic

drugs). Approximately 4 weeks later, the patient will participate in a second dosing session. In the second dosing session, 315 μg/kg psilocybin will be co-administered to the patient with either (1) a placebo (PSI + PLA), (2) low dose pimavanserin (PSI + LD), or (3) high dose pimavanserin (PSI + HD) at t = 0.

In both dosing sessions, after the patient begins to have a psychedelic experience, the patient will be asked to provide a subjective rating approximately every 20 minutes of his or her experience intensity, blissfulness, and anxiety. Physiological measures of sympathetic simulation will be measured at t = 2-3 hours. At t = 7 hours, 11D-ASC (11-Dimension Altered States of Consciousness), PANAS (Positive and Negative Affect Schedule), EDI (Ego-Dissolution Inventory) & blood cortisol will be evaluated. Longer term effects on well being will also be evaluated after the psychological experience has ended.

Functional mMRI (fMRI) will also be used to measure the effects of low and high dose pimavanserin in these patients. Individuals in each group (PSI + PLA, PSA +LD, PSI + HD) will be randomized for resting state fMRI scanning at the peak of the experience. Brain regions associated with fear, panic, and anxiety will be examined. The following comparisons will be performed: (PSI + PLA) vs (PSI + LD) vs (PSI + HD). It is hypothesized that activation in fear regions will decrease disproportionately to other neural correlates of the psychedelic state due to co-administration of pimavanserin.

Example 13: Effect of pimavanserin or ketanserin on 5-HT$_{2A}$ receptor binding by psilocybin

The following example provides details of a study used to determine whether pimavanserin or ketanserin induced changes in subjective experience during psilocybin therapy are due to changes in **5-HT$_{2A}$** occupancy. If not, downstream molecular and cellular effects that may be important in psilocybin's therapeutic effects may be preserved after co-treatment with a **5-HT$_{2A}$** specific antagonist and/or inverse agonist.

In this study, [^{11}C]CIMBI-36 (a selective 5-HT$_{2A}$ receptor agonist positron emission tomography (PET radioligand) will be used to investigate whether 5-HT$_{2A}$ binding is affected by placebo vs. pimavanserin or ketanserin

At time t = 0, patients will be administered 25 mg psilocybin (PSI) in combination with either a placebo, or a low or high dose of pimavanserin or ketanserin. At t = 2 hours, patients will be given a tracer dose of [^{11}C]CIMBI-36. At t = 2-3 hours, a PET scan will be performed, to determine whether 5-HT$_{2A}$ binding is affected by either dose of pimavanserin or ketanserin.

* * * * * *

All, documents, patents, patent applications, publications, product descriptions, and protocols which are cited throughout this application are incorporated herein by reference in their entireties for all purposes.

The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Modifications and variation of the above-described embodiments of the invention are possible without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

CLAIMS

1. A method of treating depression in a suoject in need thereof, the method comprising administering an effective amount of psilocybin or an active metabolite thereof to the subject.

2. The method of claim 1, wherein the subject has major depressive disorder, atypical depression, bipolar disorder, catatonic depression, a depressive disorder due to a medical condition, postpartum depression, premenstrual dysphoric disorder, or seasonal affective disorder.

3. The method of claim 2, wherein the subject has major depressive disorder.

4. The method of claim 2, wherein the subject has bipolar disorder.

5. The method of claim 4, wherein the subject has bipolar disorder I.

6. The method of claim 4, wherein the subject has bipolar disorder II.

7. The method of any one of claims 1-6, wherein the depression is resistant to treatment.

8. The method of any one of claims 1-7, wherein at least one sign or symptom of depression is reduced.

9. The method of claim 8, wherein the sign or symptom of depression is depressed mood, diminished interest in activities, weight loss or gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate or indecisiveness, or suicidal ideation or behavior.

10. The method of claim 9, wherein the sign or symptom of depression is measured according to a diary assessment, an assessment by clinician or caregiver, a clinical rating scale, or by functional MRI.

11. The method of claim 10, wherein the clinical depression rating scale is a Quick Inventory of Depressive Symptomatology (QIDS)-16 scale, a QIDS-16 daily scale, a Hamilton Depression Rating scale, a Beck Depression Inventory scale, a Montgomery-Asberg Depression Rating Scale, a Clinical Global Impression Scale, a Zung Self-Rating Depression Scale, a Raskin Depression Rating Scale, and/or Young Mania Rating Scale.

12. The method of claim 10, wherein the sign or symptom of depression is measured using a Spielberger's Trait and Anxiety Inventory, a Generalized Anxiety Disorder 7-Item Scale, a Warwick-Edinburgh Mental Wellbeing Scale, a Flourishing Scale, a Snaith Hamilton Anhedonia Pleasure Scale, a Life Orientation Test, a Meaning in Life Questionnaire, a Brief Resilience Scale, a Dysfunctional Attitudes Scale, a 44-item Big Five Inventory, a Peters 21-item Delusional Inventory, an Examination of Anomalous Self- Experience, a Ruminative Responses Scale, a White Bear Suppression Inventory, a Barrett Impulsivity Scale, a Brief Experiential Avoidance Questionnaire, a Modified Tellegen Absorption Questionnaire, a Scale to Assess Therapeutic Relationship, Credibility/Expectancy Questionnaire, a Connectedness to Nature Scale, a Political Perspective Questionnaire, a Social Connectedness Scale, a Bech-Rafaelsen Mania Rating Scale, a Revised Santa Clara brief compassion scale, a Gratitude Questionnaire, a Short Suggestibility Scale, a Rosenberg Self-Esteem Scale, a Universality Subscale of the Spiritual Transcendence Scale, an Oxford Questionnaire on the Emotional Side-effects of Antidepressants, a Lauks Emotional Intensity Scale, Sexual Dysfunction Questionnaire, a Brief Index of Sexual Functioning for Women, a Sexual Perceptions Questionnaire, a Barnes Akathisia Rating Scale, a Work Productivity and Activity Impairment Questionnaire, a Work and Social Adjustment Scale, a Connectedness Questionnaire, a Standard Assessment of Personality, a Positive and Negative Syndrome Scale, a Mastery Insight Scale, a Self-Reflection and Insight Scale, a Psychological Insight Scale, a Metaphysical Beliefs Questionnaire, a Spiritual Bypassing Scale, an Adverse Childhood Experience Questionnaire, a Therapeutic Music Experience Questionnaire, a Setting Questionnaire, an Absorption in Music Scale, a Psychedelic Predictor Scale, a Surrender Scale, a EuroQOL-5 Dimension-3 Level Scale, a Columbia-Suicide Severity Rating Scale, a Suicidal Ideation Attributes Scale, or any combinations thereof.

13. The method of claim 10, wherein the functional MRI measures the amygdala blood oxygen level-dependent (BOLD) response.

14. The method of claim 13, wherein the BOLD response is measured at resting state, in response to emotional faces, and/or music as a hedonic stimulus.

15. The method of any one of claims 1-14, wherein at least one sign or symptom of depression is alleviated within 24 hours of administration of the psilocybin.

16. The method of any one of claims 1-14, wherein at least one symptom of depression is alleviated within 1 week of administration of the psilocybin.

17. The method of any one of claims 1-14, wherein at least one symptom of depression is alleviated for a period of at least 1 month after administration of the psilocybin.

18. The method of any one of claims 1-14, wherein the at least one symptom of depression is alleviated for a period of at least 3 months after administration of the psilocybin.

19. The method of any one of claims 1-14, wherein the at least one symptom of depression is alleviated for a period of at least 12 months after administration of the psilocybin.

20. The method of any one of claims 1-19, wherein no other treatment is administered to the subject to reduce the sign or symptom of depression after administration of the psilocybin.

21. The method of any one of claims 1-19, wherein the method further comprises administering to the subject at least one additional therapeutic to reduce the sign or symptom of depression.

22. The method of claim 21, wherein the at least one additional therapeutic is a selective serotonin reuptake inhibitor, a serotonin and norepinephrine reuptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, a dopamine reuptake inhibitor, a 5-HT|| receptor antagonist, a 5-HT| receptor antagonist, a 5-HT receptor antagonist, a monoamine oxidase inhibitor, or a noradrenergic antagonist.

23. The method of claim 21 or 22, wherein the at least one additional therapeutic is administered prior to administration of psilocybin.

24. The method of claim 21 or 22, wherein the at least one additional therapeutic is administered after administration of psilocybin.

25. The method of claim 21 or 22, wherein the at least one additional therapeutic is administered on the same day as the psilocybin.

26. The method of any one of claims 1-25, wherein the subject has no prior psilocybin exposure.

27. The method of any one of claims 1-25, wherein the subject has prior psilocybin exposure.

28. The method of any one of claims 1-27, wherein the subject has an additional comorbidity or disorder.

29. The method of claim 28, wherein the subject has an anxiety disorder, an obsessive-compulsive disorder, alcoholism, a personality disorder, a cardiovascular disease, a neurological disease, or cancer.

30. The method of claim 29, wherein the neurological disease is dementia, Alzheimer's Disease, or Parkinson's Disease.

31. The method of any one of claims 28-30, wherein reducing at least one sign or symptom of depression in the subject treats or prevents one or more comorbidities or disorders in the subject.

32. The method of any one of claims 1-31, wherein the subject is a mammal.

33. The method of claim 32, wherein the subject is human.

34. The method of any of claims 1-33, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin comprises at least 90% by weight of Polymorph A.

35. The method of claim 34, wherein the crystalline psilocybin comprises at least 95% by weight of Polymorph A.

36. The method of claim 34 or 35, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

37. The method of any one of claims 1-33, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

38. The method of claim 37, wherein the highly pure crystalline psilocybin comprises at least 90% by weight of Polymorph A.

39. The method of claim 38, wherein the highly pure crystalline psilocybin comprises at least 95% by weight of Polymorph A.

40. The method of any one of claims 34-39, wherein the highly pure crystalline psilocybin is further characterized having either: (i) a water content of <0.5% w/w; or (ii) <0.5% w/w loss in the TGA thermogram between 25° C and 200° C.

41. The method of any one of claims 34-40, wherein the highly pure crystalline psilocybin is further characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 145°C and 155°C and a second onset temperature of between 205 and 220°C.

42. The method of any one of claims 34-41 , wherein the highly pure crystalline psilocybin is further characterized by one or more of the following: (a) a loss on drying of no more than 2% w/w; (b) residue on ignition of no more than 0.5% w/w; (c) assay (on a dry basis) of 95-103% by weight as measured by HPLC; (d) residual solvent content of no more than 3000 ppm methanol; 5000 ppm ethanol, 720 ppm THF, and 890 ppm toluene, as measured by HRGC; (e) phosphoric acid content of no more than 1% w/w as measured by ^{31}P NMR; and (f) Inductively Coupled Plasma Mass Spectrometry (ICP-MS) elemental analysis of: (i) no more than 1.5ppm Cd; (ii) no more than 1.5ppm Pb; (iii) no more than 4.5ppm As; (iv) no more than 9.0ppm Hg; (v) no more than 15ppm Co; (vi) no more than 30ppm V; (vii) no more than 60ppm Ni; (viii) no more than 165ppm Li; and (ix) no more than 30ppm Pd.

43. The method of any one of claims 34-42, wherein the highly pure crystalline psilocybin has no single impurity of greater than 0.5%.

44. The method of any of claims 34-43, wherein the dosage form further comprises about 5 to 40 mg of the highly pure crystalline psilocybin.

45. The method of claim 44, wherein the dosage form comprises 5 mg of highly pure crystalline psilocybin.

46. The method of claim 44, wherein the dosage form comprises about 10 mg of highly pure crystalline psilocybin.

47. The method of claim 44, wherein the dosage form comprises about 35 mg of highly pure crystalline psilocybin.

48. The method of any one of claims 34-47, wherein the dosage form comprises silicified microcrystalline cellulose.

49. The method of claim 48, wherein the silicified microcrystalline cellulose has a particle size range from about 45 to 150 microns.

50. The method of any one of claims 34-49, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns and the second variant has a particle size of about 90 to 150 microns.

51. The method of claim 50, wherein about 30% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 70% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

52. The method of claim 50, wherein about 20% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 80% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

53. The method of claim 50, wherein about 15% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 85% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

54. The method of claim 53, wherein the dosage form comprises 5 mg of crystalline psilocybin in the form of Polymorph A, 12.5 mg of SMCC 50, 79.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide and 1 mg sodium stearyl fumarate.

55. The method of claim 53, wherein the dosage form comprises 1 mg of crystalline psilocybin in the form of Polymorph A, 20.5 mg of SMCC 50, 75.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide, and 1 mg sodium stearyl fumarate.

56. The method any one of claims 34-55, wherein the dosage form is an oral dosage form.

57. The method claim 56, wherein the dosage form is a capsule.

58. The method claim 56, wherein the dosage form is a tablet.

59. The method of any one of claims 1-58, wherein at least one dose of psilocybin is administered to the subject.

60. The method of claim 59, wherein the at least dose of psilocybin is in the range of about 0.1 mg to about 100 mg.

61. The method of claim 60, wherein the dose of psilocybin is about 1 mg.

62. The method of claim 60, wherein the dose of psilocybin is about 10 mg.

63. The method of claim 60, wherein the dose of psilocybin is about 25 mg.

64. The method of any one of claims 1-58, wherein more than one dose of psilocybin is administered to the subject.

65. The method of claim 65, wherein at least two doses of psilocybin are administered to the subject.

66. The method of any one of claims 64-65, wherein the psilocybin is administered once per day.

67. The method of any one of claims 64-65, wherein the psilocybin is administered at least once per week.

68. The method of any one of claims 64-65, wherein the psilocybin is administered at least twice per week.

69. The method of any one of claims 64-65, wherein the psilocybin is administered at least once per month.

70. The method of any one of claims 64-65, wherein the psilocybin is administered at least twice per month.

71. The method of any one of claims 64-65, wherein the psilocybin is administered at least once every three months.

72. The method of any one of claims 64-65, wherein the psilocybin is administered at least once every six months.

73. The method of any one of claims 64-65, wherein the psilocybin is administered at least once every 12 months.

74. The method of any one of claims 64-73, wherein each dose of psilocybin administered is in the range of about 0.1 mg to about 100 mg.

75. The method of claim 74, wherein each dose of psilocybin administered is about 1 mg.

76. The method of claim 74, wherein each dose of psilocybin administered is about 10 mg.

77. The method of claim 74, wherein each dose of psilocybin administered is about 25 mg.

78. The method of any one of claims 59-77, wherein the psilocybin is administered by one of the following routes: oral, intravenous, intramuscular, parenteral, topical, inhalation, rectal, transmucosal, intranasal, buccal, vaginal, intrathecal, intraocular, transdermal, in utero, intralymphatic, or by direct tissue or organ injection.

79. The method of claim 78, wherein the psilocybin is administered orally.

80. The method of any one of claims 1-79, wherein the subject participates in at least one psychological support session before administration of the psilocybin.

81. The method of claim 80, wherein the subject participates in at least three psychological support sessions before administration of the psilocybin.

82. The method of any one of claims 80-81 , wherein the at least one therapeutic intention is discussed during the psychological support session.

83. The method of any one of claims 80-82, wherein self-directed inquiry and experiential processing are practiced during the psychological support session.

84. The method of any one of claims 80-83, wherein the subject participates in at least one psychological support session after administration of the psilocybin.

85. The method of claim 84, wherein the subject participates in at least three psychological support sessions after administration of the psilocybin.

86. The method of any one of claims 80-85, wherein the psilocybin is administered to the subject in a room with a substantially non-clinical appearance.

87. The method of claim 86, wherein the room comprises soft furniture.

88. The method of claim 86, wherein the room is decorated using muted colors.

89. The method of claim 86, wherein the room comprises a high-resolution sound system.

90. The method of any one of claims 86-89, wherein the room comprises a bed or a couch.

91. The method of claim 90, wherein the subject lies in the bed or on the couch for approximately 4-8 hours, or a substantial fraction thereof, after administration of the psilocybin.

92. The method of any one of claims 86-91 , wherein the subject listens to music for approximately 4-8 hours, or a substantial fraction thereof, after administration of the psilocybin.

93. The method of any one of claims 86-92, wherein the subject wears an eye mask for approximately 4-8 hours, or a substantial fraction thereof, after administration of the psilocybin.

94. The method of any one of claims 87-93, wherein a therapist provides psychological support to the subject for approximately 4-8 hours after administration of the psilocybin.

95. The method of claim 94, wherein the therapist uses guided imagery and/or breathing exercises to calm the subject and/or focus the subject's attention.

96. The method of claim 94, wherein the therapist provides reassuring physical contact with the subject.

97. The method of claim 96, wherein the therapist holds the hand, arm, or shoulder of the subject.

98. The method of claim 94, wherein the therapist encourages the subject to perform self-directed inquiry and experiential processing.

99. The method of claim 94, wherein the therapist reminds the subject of at least one therapeutic intention.

100. The method of claim 94, wherein the therapist counsels the subject to do one or more of the following: (1) to accept feelings of anxiety, (2) to allow the experience to unfold naturally, (3) to avoid psychologically resisting the experience, (4) to relax, and/or (5) to explore the subject's own mental space.

101. The method of claim 94, wherein the therapist does not initiate conversation with the subject.

102. The method of claim 94, wherein the therapist responds to the subject if the subject initiates conversation.

103. The method of any one of claims 80-102, wherein the psychological support is provided remotely to the subject.

104. The method of claim 103, wherein the psychological support is provided via a digital or electronic system.

105. The method of claim 104, wherein the digital or electronic system is a mobile phone app.

106. The method of claim 105, wherein the digital or electronic system is a website.

107. A method as described herein.

108. A formulation as described herein.

109. Crystalline psilocybin as described herein.

110. A pharmaceutical dosage form comprising crystalline psilocybin as described herein as described herein.

111. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance-Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation

(Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, or Kleptomania.

112. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Neurocognitive Disorders due to Alzheimer's, Lewy Bodies, Traumatic Brain Injury, Prion Disease, HIV Infection, Parkinson's, or Huntington's; concussion; chronic traumatic encephalopathy (CTE); Language Disorder, Speech Sound Disorder (Phonological Disorder); Childhood-Onset Fluency Disorder (Stuttering); Social (Pragmatic) Communication Disorder; Tourette's Disorder; Persistent (Chronic) Motor or Vocal Tic Disorder; Amnestic Disorder Due to Known Physiological Condition; Transient Cerebral Ischemic Attack, Cerebral Infarction, Cerebral Bleeding, Progressive Supranuclear Ophthalmoplegia, or Retrograde Amnesia.

113. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Autism Spectrum Disorder, or Antisocial Personality Disorder.

114. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Attention-Deficit/Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder; or Unspecified Attention-Deficit/Hyperactivity Disorder.

115. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the

following diseases, disorders, or conditions: Schizotypal (Personality) Disorder, Delusional Disorder, Schizophrenia, or Schizoaffective Disorder

116. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Female Sexual Interest/Arousal Disorder, Male Hypoactive Sexual Desire Disorder, or Excessive Sexual Drive.

117. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Bipolar I Disorder, Bipolar II Disorder, or Cyclothymic Disorder.

118. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Insomnia Disorder, Hypersomnolence Disorder, Narcolepsy, or Primary Central Sleep Apnea.

119. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Schizoid Personality Disorder, Schizotypal Personality Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, or Obsessive-Compulsive Personality Disorder.

120. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: age-related hearing loss or tinnitus.

121. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Multiple Sclerosis, Cranial Nerve Disorder, Neuromyelitis Optica, Bell's Palsy, Guillain Barre Syndrome, Demyelinating Disease of Central Nervous System, or Chronic Inflammatory Demyelinating Polyneuritis.

122. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject suffers from pain.

123. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has at least one of the following diseases, disorders, or conditions: Myelopathy, Traumatic Brain Injury, Intellectual Disabilities, Mania, Neurodegeneration, Paraphilic disorders, Suicidal Behavior Disorder, Nonsuicidal Self-Injury, Persistent Complex Bereavement Disorder, GI Tract Related Diseases, Epilepsy, Sickle Cell Disease, locked-in syndrome, restless leg syndrome, stroke, or Amyotrophic Lateral Sclerosis (ALS).

124. A method of treating a subject, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein after administration the subject exhibits an improvement in cognition.

125. The method of embodiment 124 wherein the improvement in cognition is an improvement in attention, episodic memory, working memory, spatial memory, social cognition, executive function, and/or cognitive flexibility.

126. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Treatment Resistant Depression (TRD).

127. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically-effective dose of psilocybin, wherein the subject has Major Depressive Disorder (MDD).

128. The method of any one of claims 111-127 wherein the subject is a mammal.

129. The method of claims 18, wherein the subject is a human.

130. The method of any of claims 111-129, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin comprises at least 90% by weight of Polymorph A.

131. The method of claim 130, wherein the crystalline psilocybin comprises at least 95% by weight of Polymorph A.

132. The method of claim 130 or 131, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

133. The method of any of claims 111-132, wherein the psilocybin is administered in a dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%.

134. The method of any of claim 130-133, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns and the second variant has a particle size of about 90 to 150 microns.

135. The method of claim 24, wherein about 30% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 70% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

136. The method of any one of claims 130-135, wherein the dosage form is an oral dosage form.

137. The method of claim 136, wherein the dosage form is a capsule.

138. The method of claim 136, wherein the dosage form is a tablet.

139. The method of any one of claims 111-138, wherein at least one dose of psilocybin is administered to the subject.

140. The method of claim 139, wherein at least dose of psilocybin is in the range of about 0.1 mg to about 100 mg.

141. The method of claim 140, wherein the dose of psilocybin is about 25 mg.

142. The method of any one of claims 111-141, wherein the subject participates in at least one psychological support session before administration of the psilocybin.

143. The method of claim 142, wherein the subject participates in at least one psychological support session after administration of the psilocybin.

144. The method of claim 142 or 143, wherein a therapist provides psychological support to the subject for approximately 4-8 hours after administration of the psilocybin.

145. A dosage form comprising a therapeutically effective amount of highly pure crystalline psilocybin in the form of Polymorph A, wherein the crystalline psilocybin comprises at least 90% by weight of Polymorph A, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns (SMCC 50), and the second variant has a particle size of about 90 to 150 microns (SMCC 90), wherein the ratio of SMCC 50 to SMCC 90 is 1:5 to 1:8 wt%.

146. The dosage form of claim 145, further comprising a disintegrant, glidant, or lubricant.

147. The dosage form of claim 147, comprising a disintegrant, wherein the disintegrant is sodium starch glycolate at less than 3% (by wt), less than 2%, or 1% or less.

148. The dosage form of any one of claims 145-147 wherein the ratio of SMCC 50 to SMCC 90 is 1:5-1 :7; 1:6-1 :7; 1:6-1 :8; 1.7-1 .8, 1:6; 1:6.1 ; 1:6.2; 1:6.3; 1:6.4; 1:6.5; 1:6.6; 1.6.7; 1:6.8; 1.6.9; or 1:7.

149. The dosage form of any one of claims 145-147, comprising 5-40 mg of psilocybin

150. The dosage form of claim 145, comprising 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%.

151 . The dosage form of claim 145, comprising 5 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

152. The dosage form of claim 145, comprising 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%.

153. The dosage form of claim 145, comprising 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%.

154. The dosage form of claim 145, comprising comprises 10 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%. 155. The dosage form of claim 145, comprising 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 1%. 156. The dosage form of claim 145, comprising 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5% to 1.0%.

157. The dosage form of claim 145, comprising 25 mg of psilocybin and SMCC 50 and SMCC 90, wherein the ratio of SMCC 50 to SMCC 90 is 1:6.4 and sodium starch glycolate at about 0.5%.

158. The dosage form of claim 145, comprising 5 mg of crystalline psilocybin A, 12.5 mg of SMCC 50, 79.5 mg of SMCC 90, 1 mg sodium starch glycolate, 1 mg colloidal silicon dioxide and 1 mg sodium stearyl fumarate.

159. The dosage form of any one of claims 145-158, wherein the crystalline psilocybin comprises at least 95% by weight of Polymorph A.

160. The dosage form of any one of claims 145-158, wherein the dosage form is an oral dosage form.

161. The dosage form of any one of claims 145-158, wherein the dosage form is a capsule.

162. The dosage form of any one of claims 145-158, wherein the dosage form is a tablet.

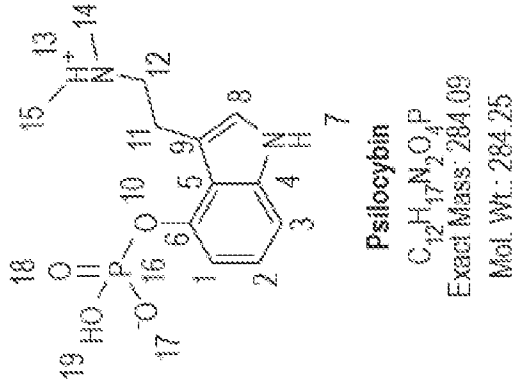


Fig. 1

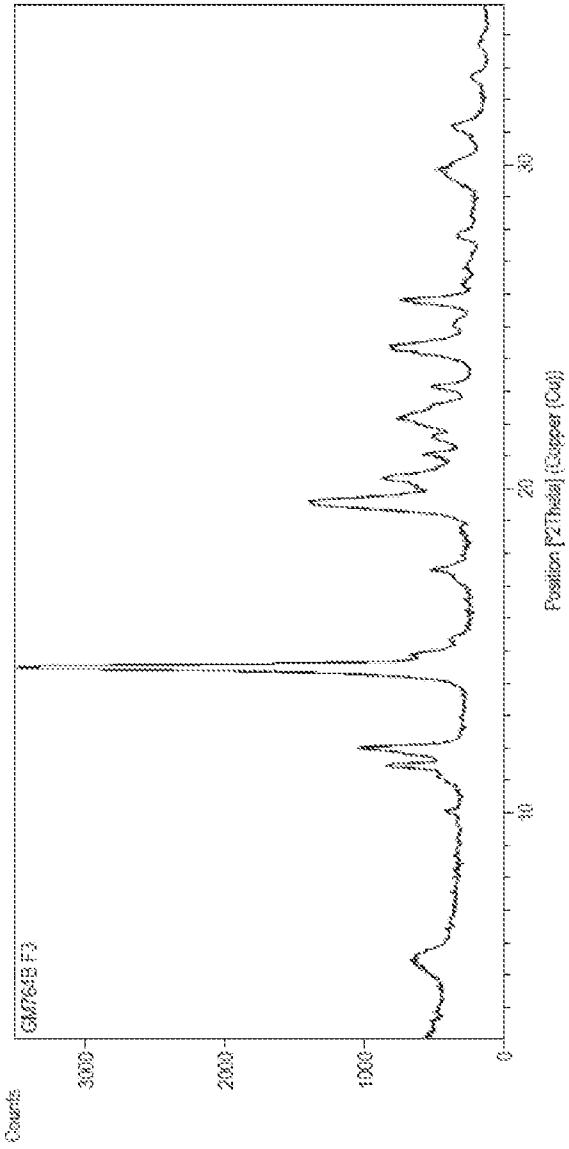
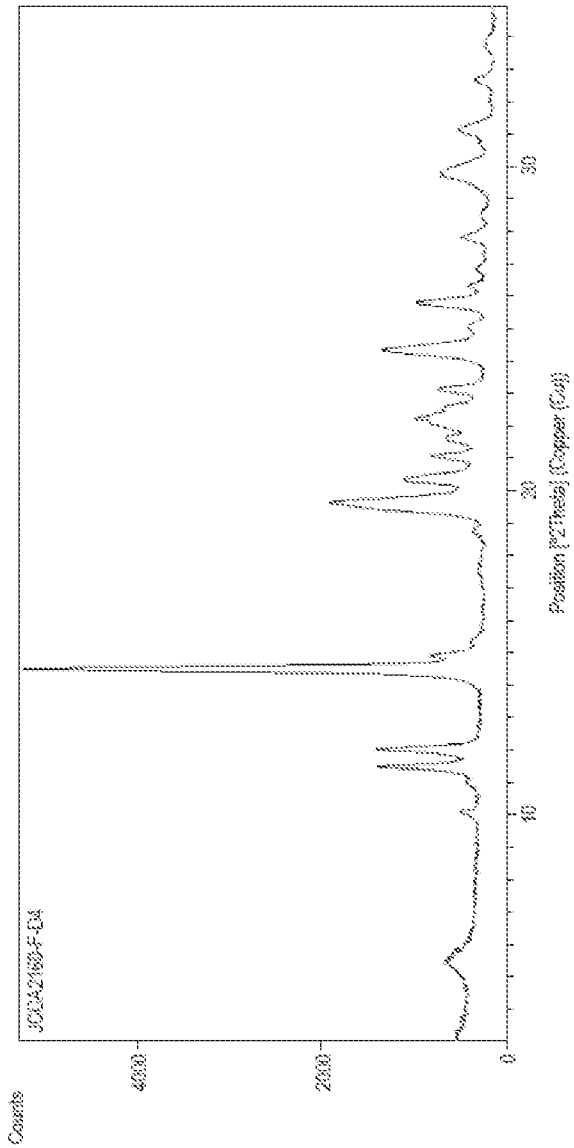

GM7645 F3
Counts
3000
2000
1000
0
10
20
30
Position [°2Theta] (Copper (Cu))

Fig. 2A

Fig. 2B


JGA216B-F-04
Counts
4000
2000
0
10
20
30
Position [°2Theta] (Copper (Cu))

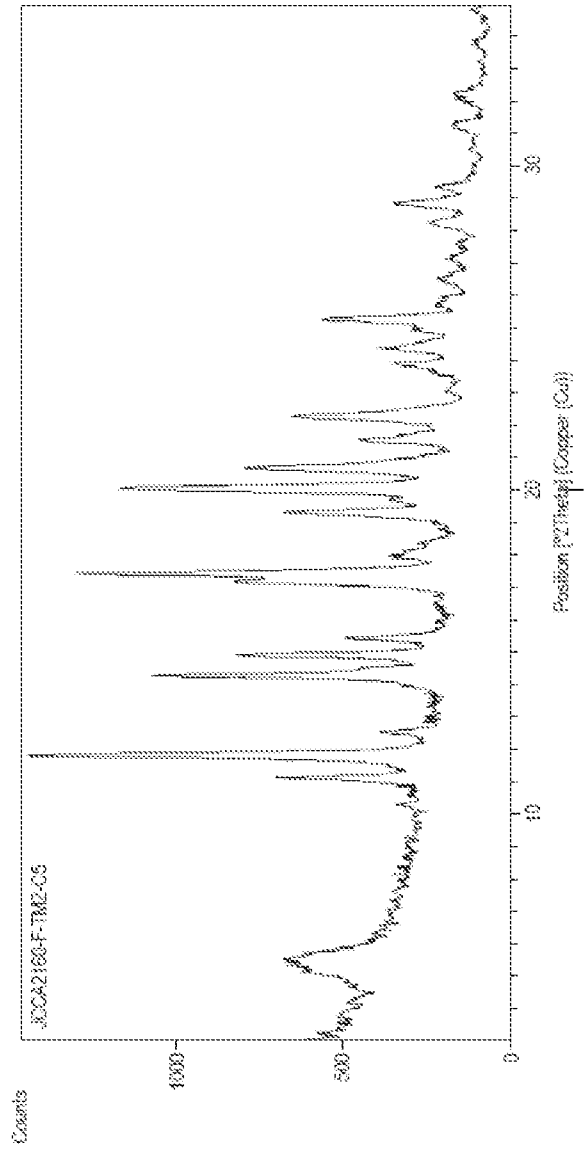

Counts
1000
500
0
10
20
30
Position [°2Theta] (Copper (Cu))
JDCA2160-F-TME-CS

Fig. 2C

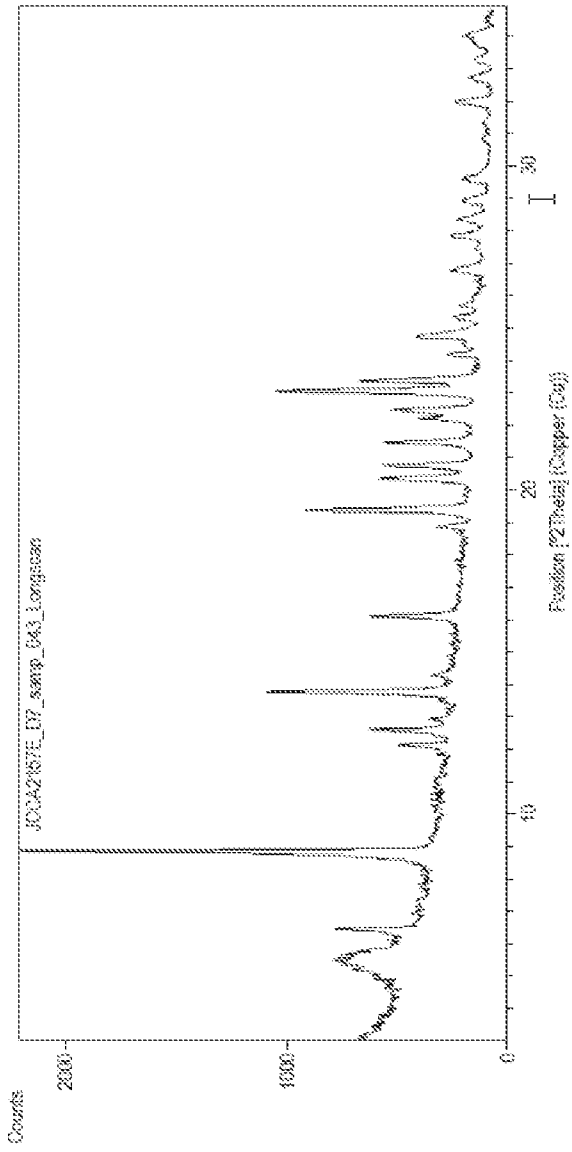

JDGA2105TE_D7_samp_043_Longbeam
Counts
2000
1000
0
10
20
30
Position [°2Theta] (Copper (Cu))

Fig. 2D

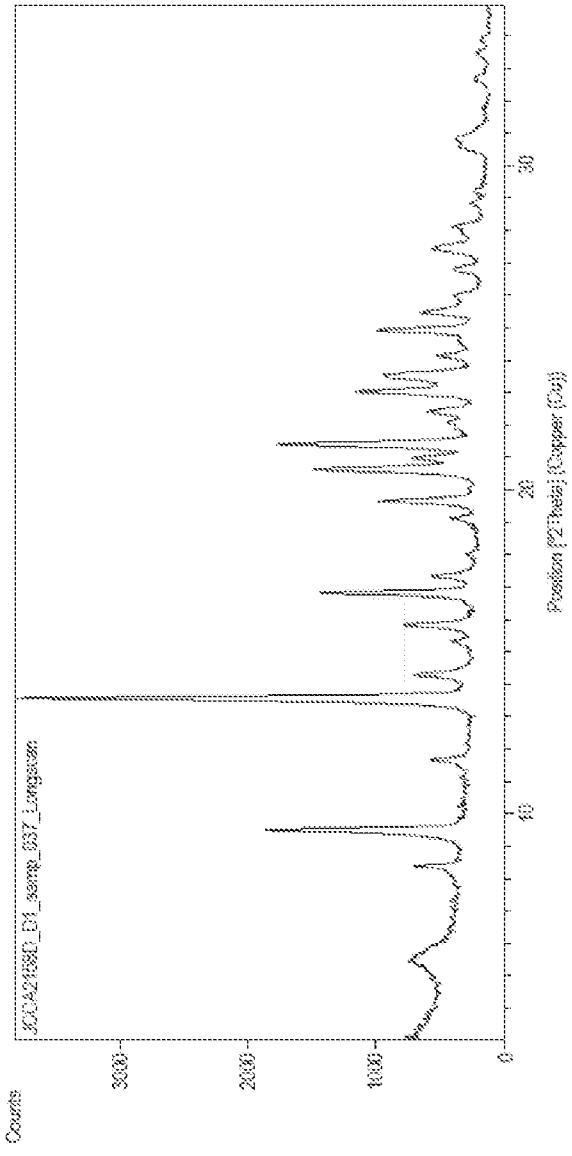
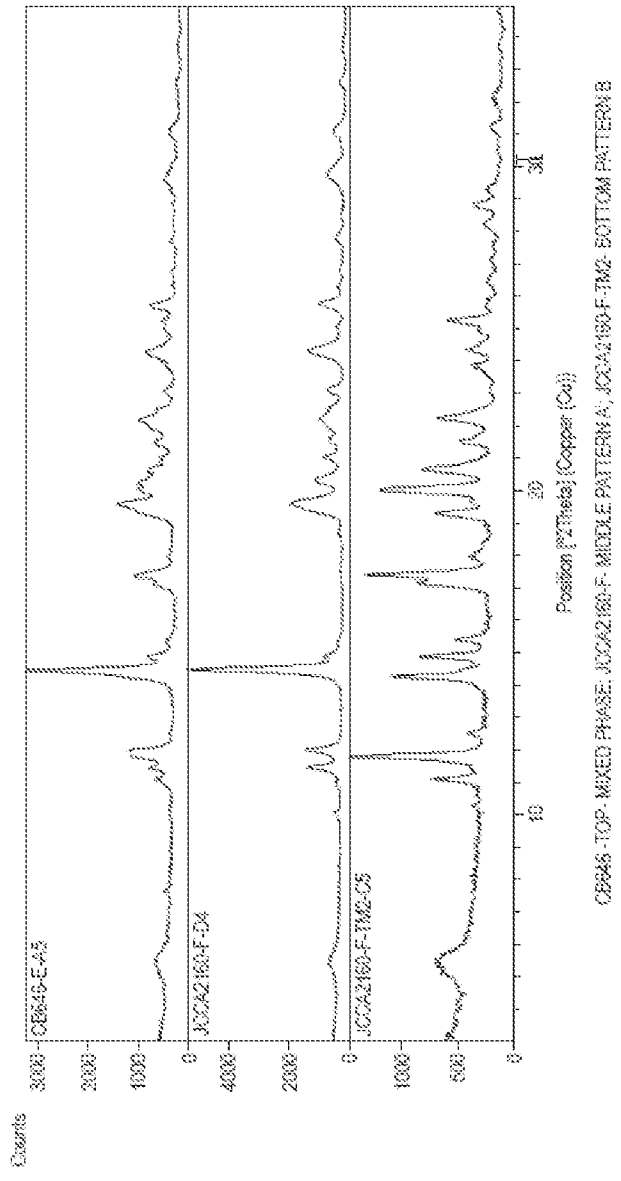


Fig. 2E

Fig. 2F


Counts
3000
2000
1000
0
CB645-E-A5
4000
2000
0
JCCA2160-F-D4
1000
500
0
JCCA2160-F-TM2-D5
10
20
30
Position (°2Theta) (Copper (Cu))
CB645 -TOP- MIXED PHASE; JCCA2160-F- MIDDLE PATTERN A; JCCA2160-F-TM2- BOTTOM PATTERN B

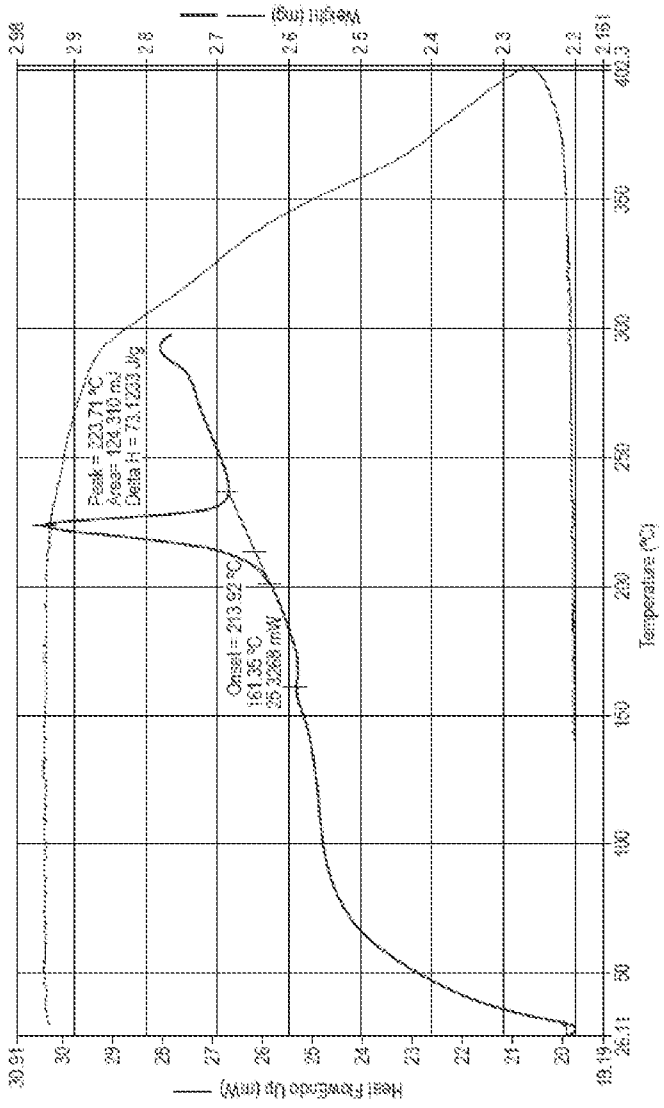

Peak = 223.71 °C
Area= 124.310 mJ
Delta H = 73.1233 J/g
Onset = 213.92 °C
181.35 °C
35.3288 mW
Temperature (°C)
Heat flow Endo Up (mW)
Weight (mg)

Fig. 3A

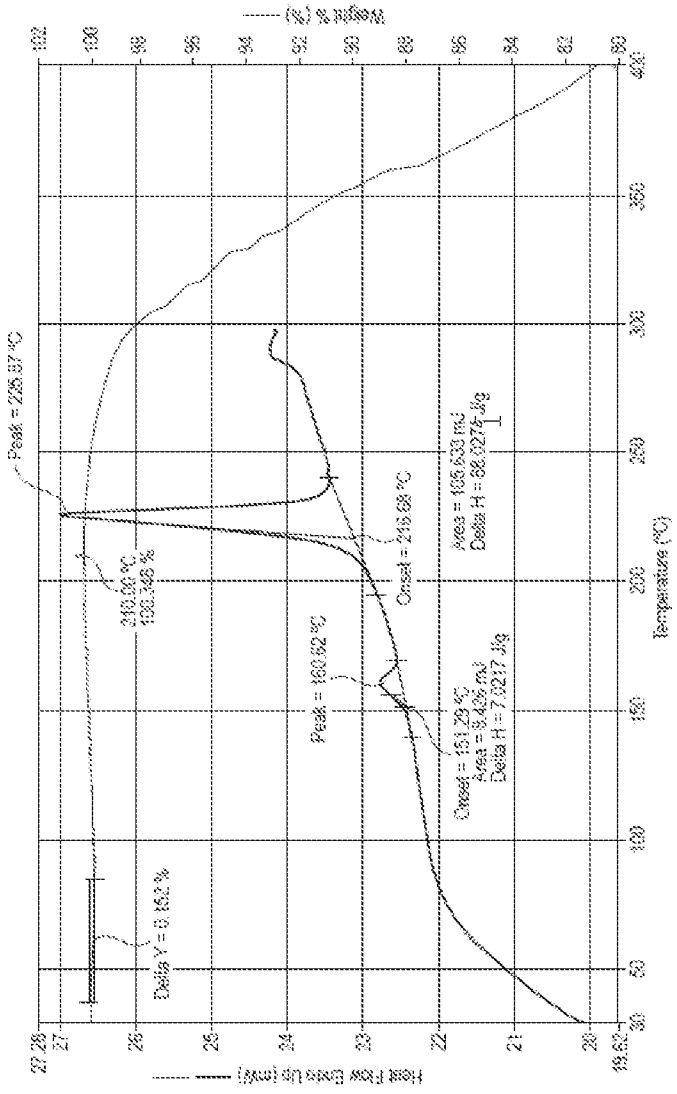

Peak = 226.87 °C
210.60 °C
133.348 %
Delta Y = 6.152 %
Peak = 160.62 °C
Onset = 215.68 °C
Area = 105.633 mJ
Delta H = 86.0275 J/g
Onset = 151.29 °C
Area = 9.435 mJ
Delta H = 7.0217 J/g
Temperature (°C)
Heat Flow Endo Up (mW)
Weight (%)

Fig. 3B

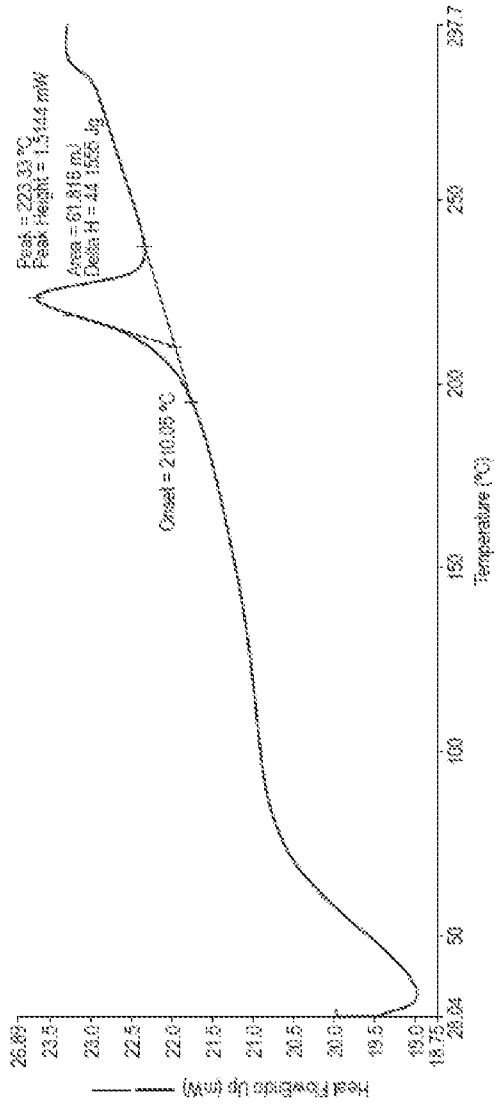

Peak = 223.33 °C
Peak Height = 1.5144 mW
Area = 61.818 mJ
Delta H = 44.1555 J/g
Onset = 210.05 °C
Heat Flow Endo Up (mW)
Temperature (°C)
26.89
23.5
23.0
22.5
22.0
21.5
21.0
20.5
20.0
19.5
19.0
18.75
28.04
50
100
150
200
250
297.7

Fig. 3C

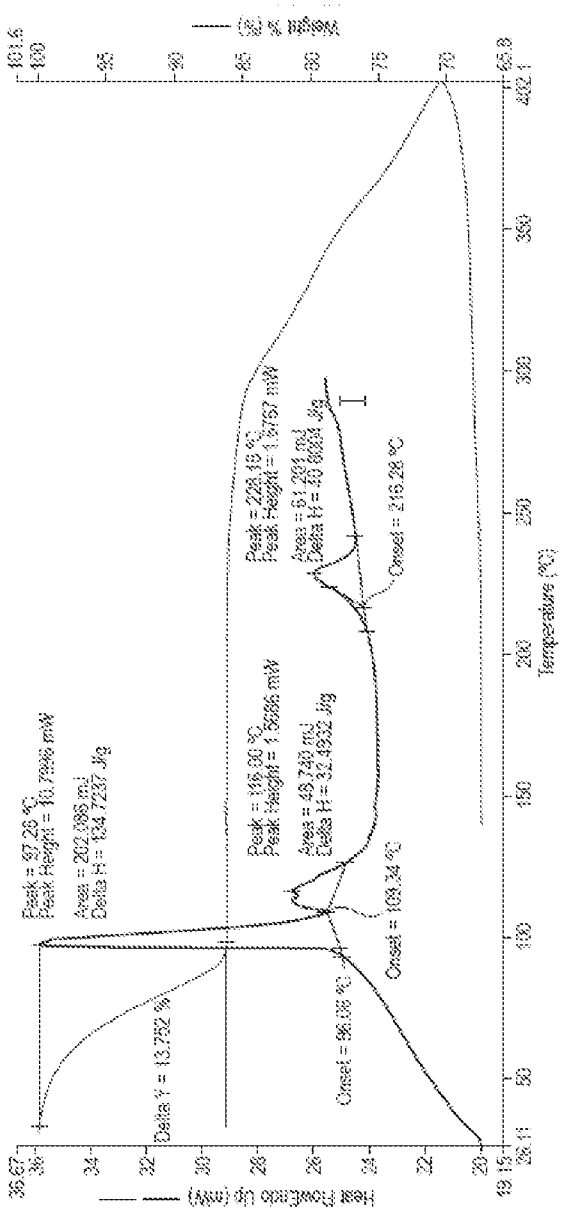

Peak = 97.26 °C
Peak Height = 10.7866 mW
Area = 262.086 mJ
Delta H = 134.7237 J/g
Delta Y = 13.752 %
Onset = 96.186 °C
Peak = 116.30 °C
Peak Height = 1.5266 mW
Area = 49.740 mJ
Delta H = 32.4932 J/g
Onset = 103.34 °C
Peak = 228.19 °C
Peak Height = 1.6767 mW
Area = 61.201 mJ
Delta H = 40.0004 J/g
Onset = 216.29 °C
Heat flow Endo Up (mW)
Temperature (°C)
Weight (%)

Fig. 3D

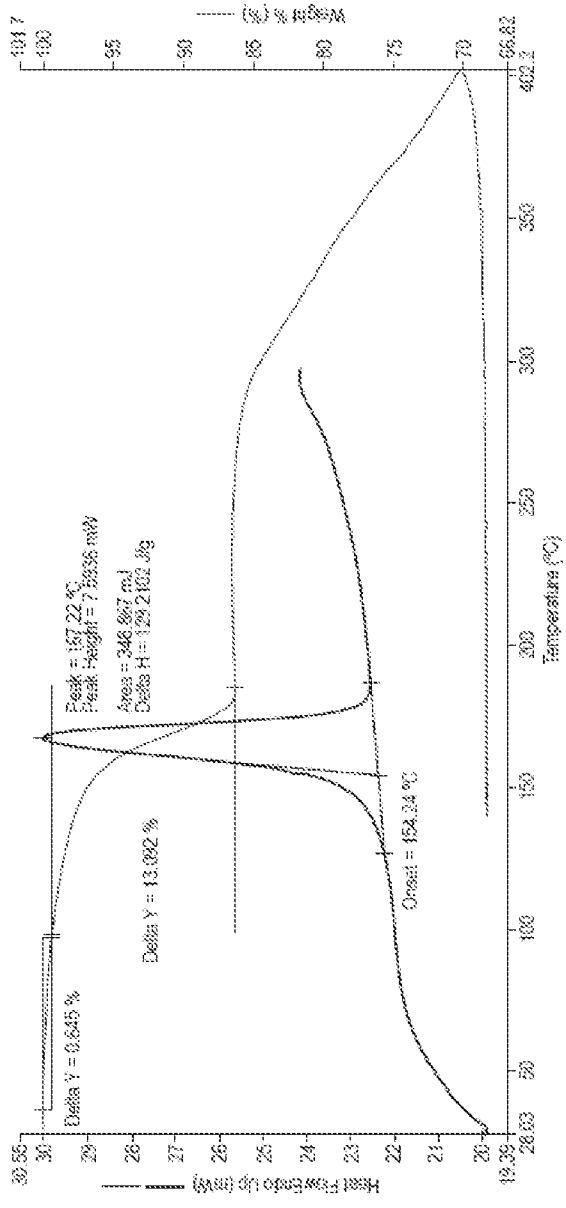

Peak = 167.22 °C
Peak Height = 7.8336 mW
Area = 346.867 mJ
Delta H = 129.2183 J/g
Delta Y = 13.092 %
Delta Y = 0.645 %
Onset = 154.34 °C
Temperature (°C)
Heat Flow Endo Up (mW)
Weight (%)

Fig. 3E

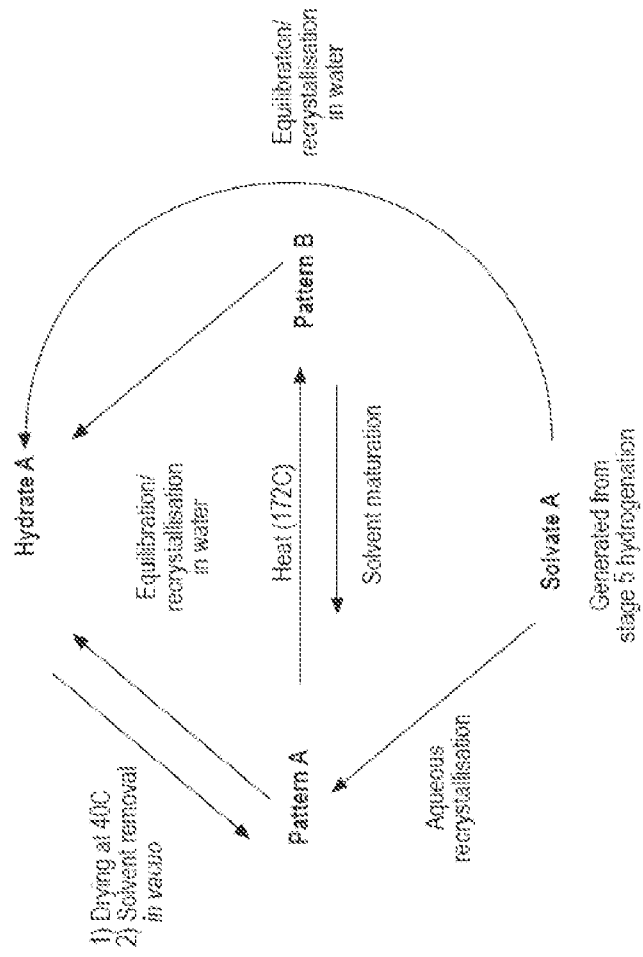

Equilibration/
recrystallisation
in water
Pattern B
Hydrate A
Equilibration/
recrystallisation
in water
Heat (172C)
Solvent maturation
Solvate A
Generated from
stage 5 hydrogenation
1) Drying at 40C
2) Solvent removal
in vacuo
Pattern A
Aqueous
recrystallisation

Fig. 4

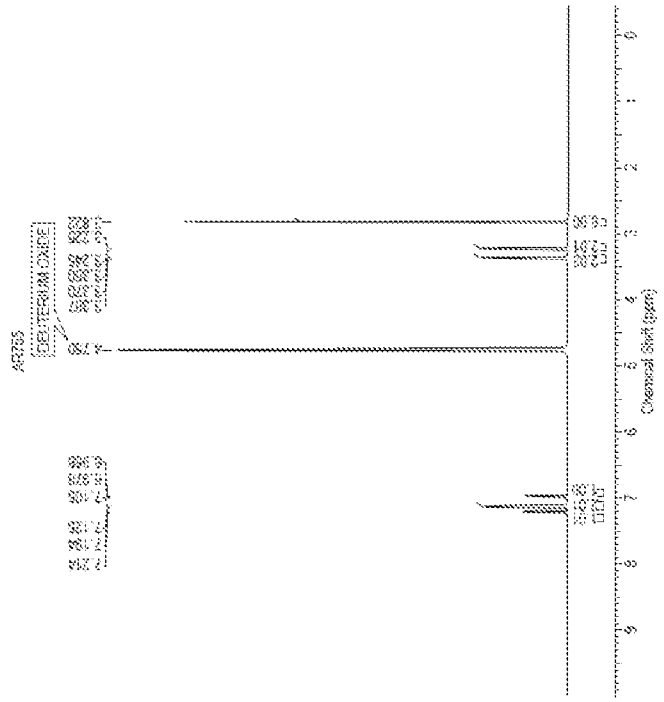


Fig. 5

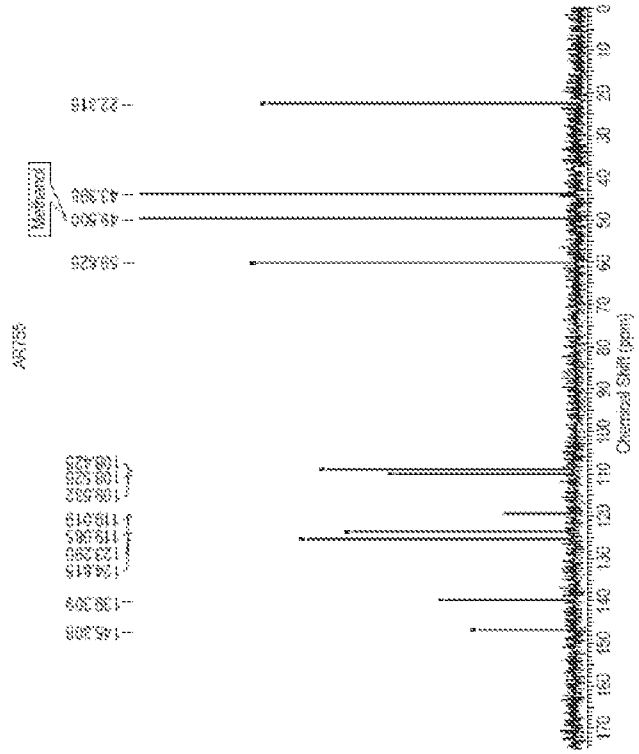


Fig. 6

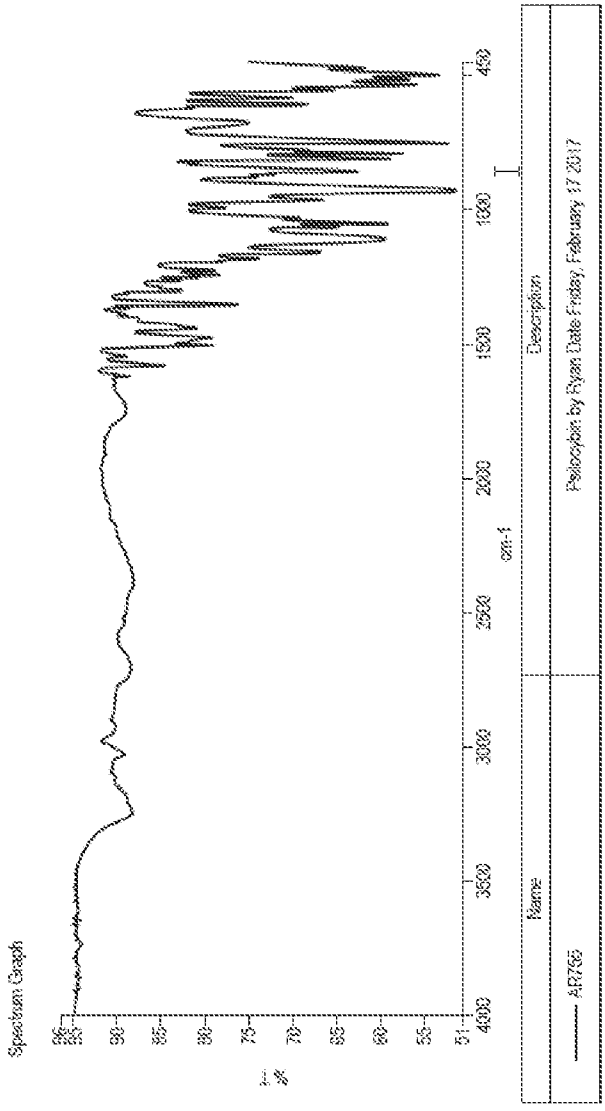

Spectrum Graph
%T
cm-1
4000
3500
3000
2500
2000
1500
1000
450
Name
AR765
Description
Pelicophen by Ryan Date: Friday, February 17 2017

Fig. 7

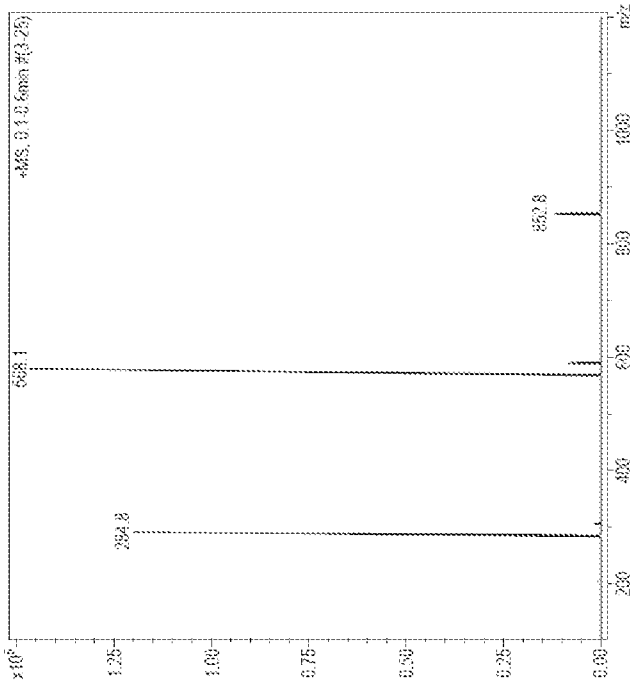
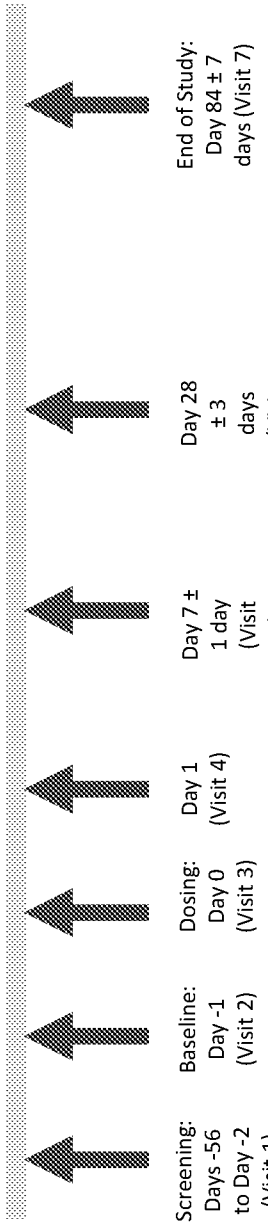

x10⁶
1.25
1.00
0.75
0.50
0.25
0.00
294.8
608.1
852.8
200
400
600
800
1000
m/z

Fig. 8

Fig. 9A


Screening: Days -56 to Day -2 (Visit 1)
Baseline: Day -1 (Visit 2)
Dosing: Day 0 (Visit 3)
Day 1 (Visit 4)
Day 7 ± 1 day (Visit 5)
Day 28 ± 3 days (Visit 6)
End of Study: Day 84 ± 7 days (Visit 7)

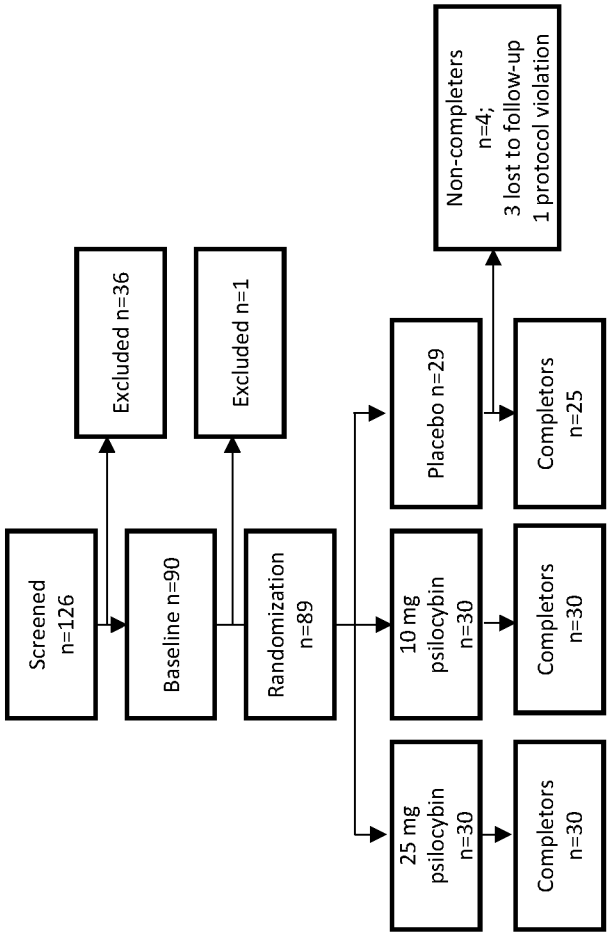

Screened n=126
Excluded n=36
Baseline n=90
Excluded n=1
Randomization n=89
Placebo n=29
Non-completers n=4; 3 lost to follow-up 1 protocol violation
Completors n=25
10 mg psilocybin n=30
Completors n=30
25 mg psilocybin n=30
Completors n=30

Fig. 9B

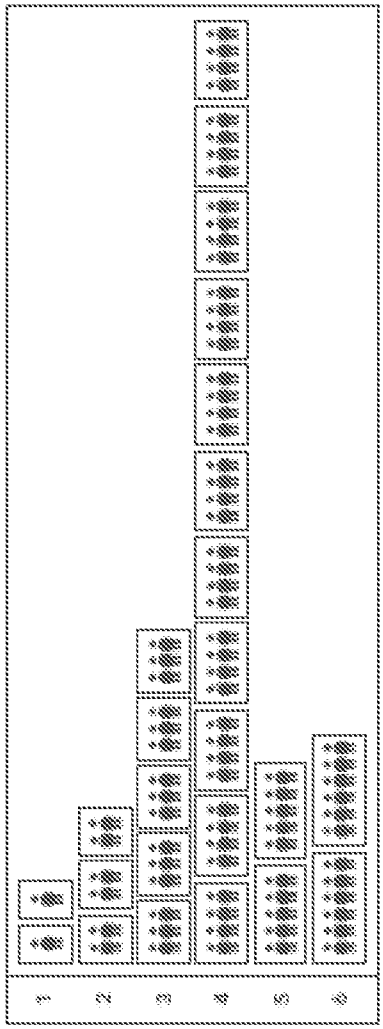


Fig. 9C

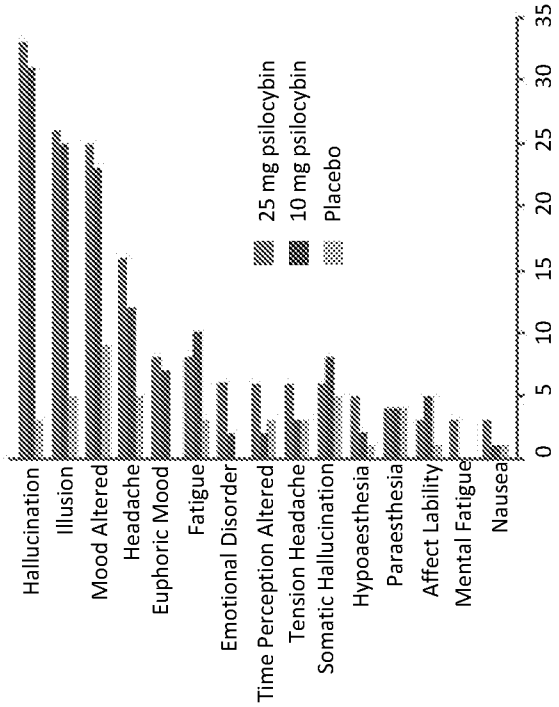

Hallucination
Illusion
Mood Altered
Headache
Euphoric Mood
Fatigue
Emotional Disorder
Time Perception Altered
Tension Headache
Somatic Hallucination
Hypoaesthesia
Paraesthesia
Affect Lability
Mental Fatigue
Nausea
25 mg psilocybin
10 mg psilocybin
Placebo
0
5
10
15
20
25
30
35

Fig. 9D

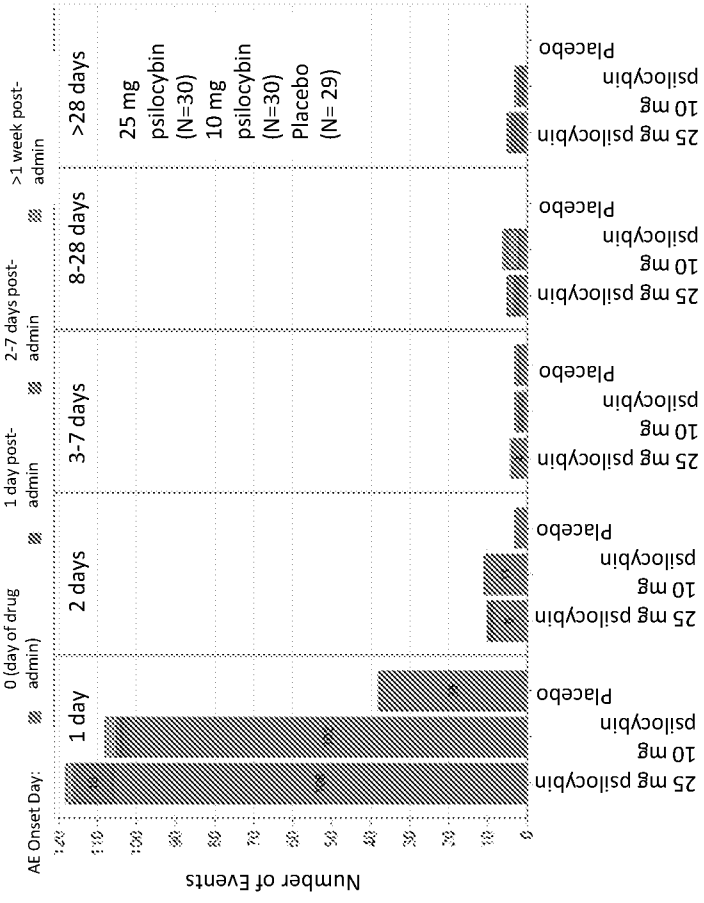

AE Onset Day:
1 day
2 days
3-7 days
8-28 days
>28 days
0 (day of drug admin)
1 day post-admin
2-7 days post-admin
>1 week post-admin
25 mg psilocybin (N=30)
10 mg psilocybin (N=30)
Placebo (N= 29)
Number of Events
25 mg psilocybin
10 mg psilocybin
Placebo

Fig. 9E

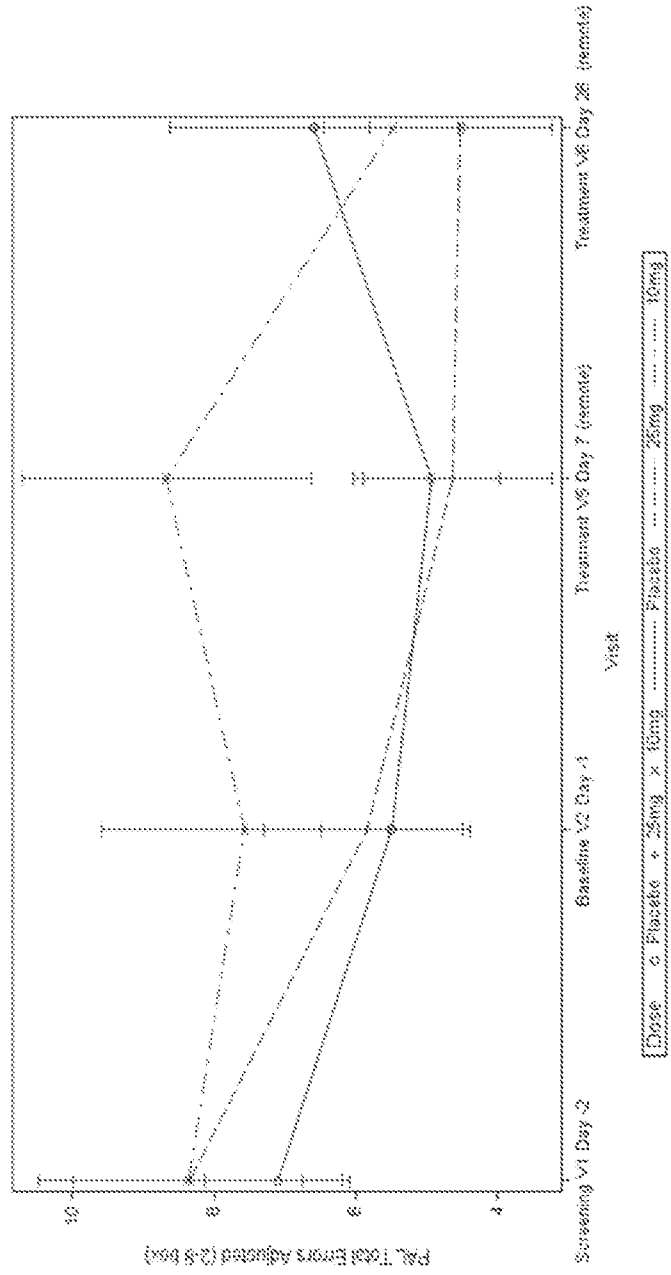
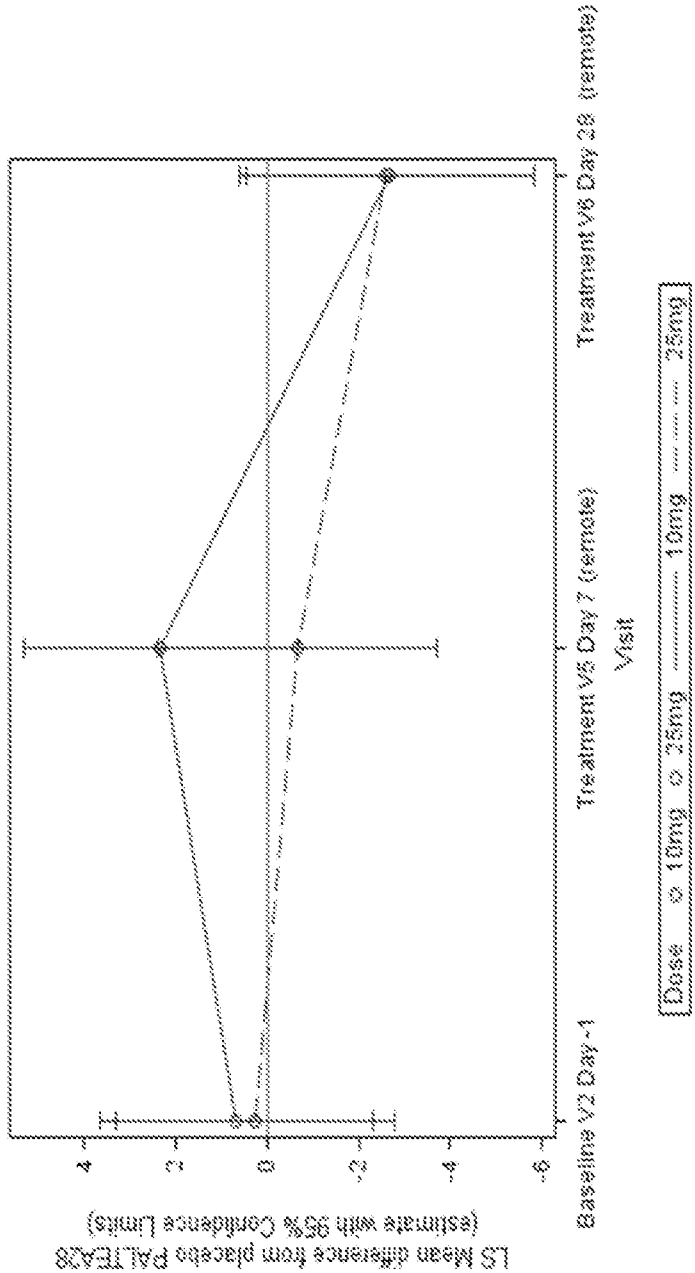

PAL Total Errors Adjusted (2-8 box)
Visit
Screening V1 Day -2
Baseline V2 Day 1
Treatment V6 Day 7 (remote)
Treatment V8 Day 28 (remote)
Dose
c. Placebo
25mg
50mg
Placebo
25mg
50mg

Fig. 9F

Fig. 9G


LS Mean difference from placebo PALTEA38
(estimate with 95% Confidence Limits)
4
2
0
-2
-4
-6
Baseline V2 Day -1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose 10mg 25mg 10mg 25mg

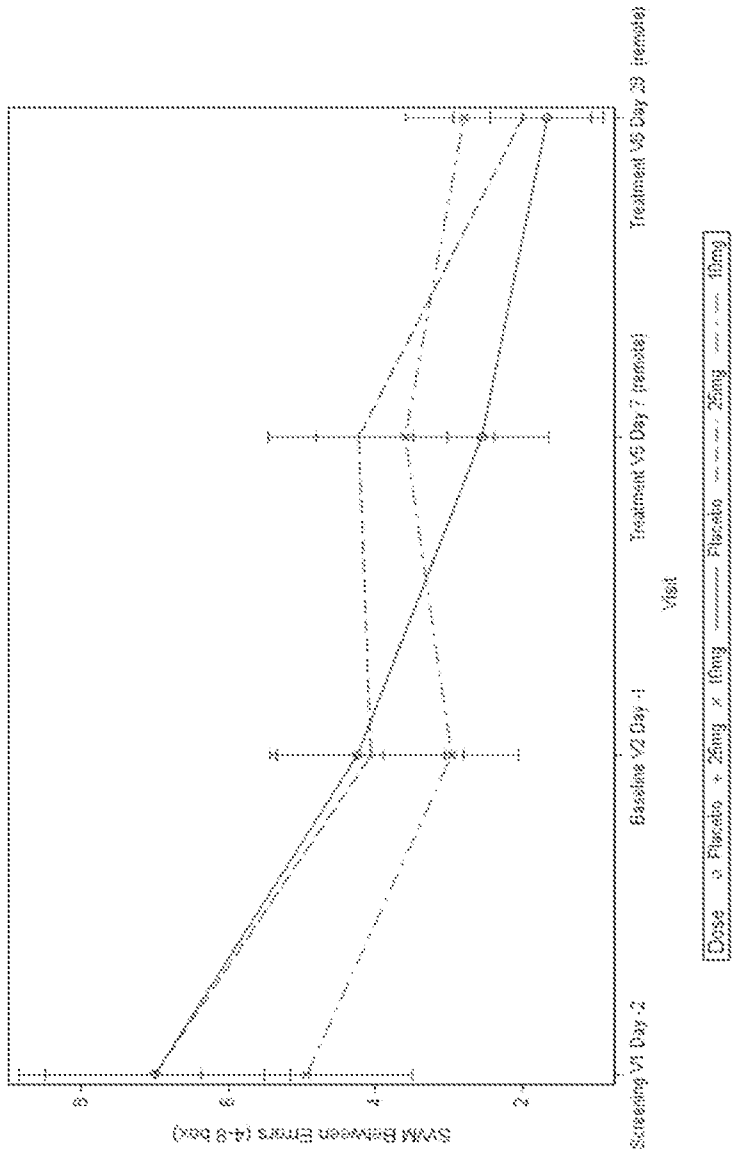

SVMs Between Errors (4-8 bpm)
8
6
4
2
Screening V1 Day -2
Baseline V2 Day 1
Treatment V3 Day 7 (interim)
Treatment V5 Day 23 (end)
Visit
Dose
Placebo
25mg
10mg
Placebo
25mg
10mg

Fig. 9H

Fig. 9I

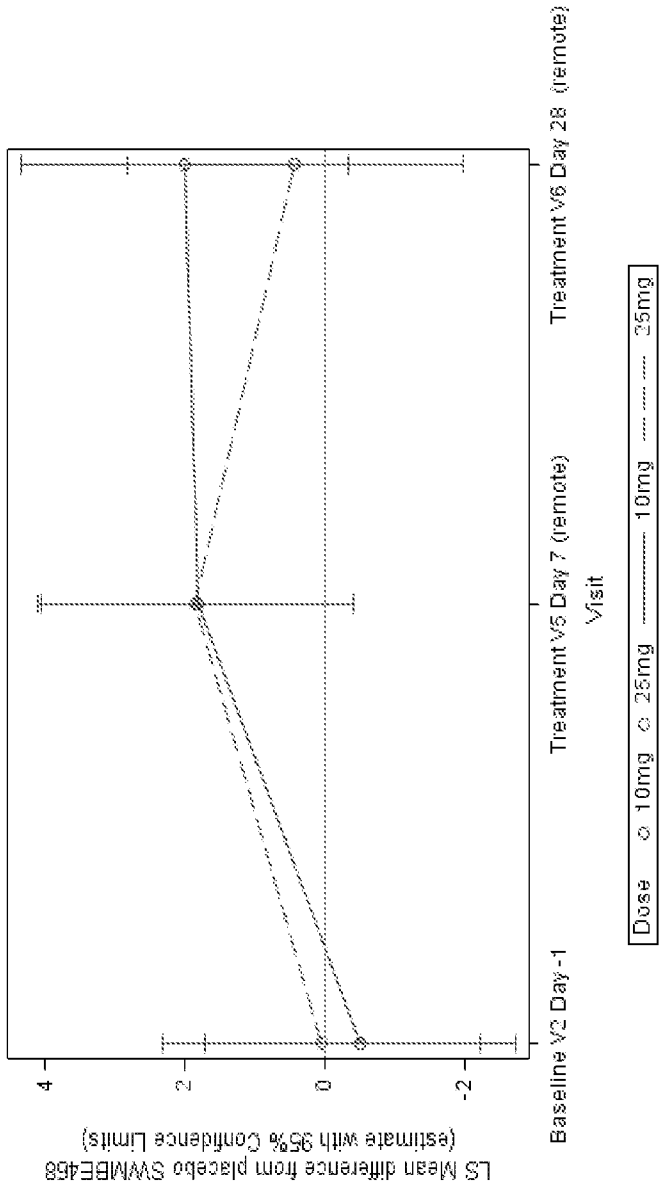

LS Mean difference from placebo SWMBE458
(estimate with 95% Confidence Limits)
4
2
0
-2
Baseline V2 Day -1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose 10mg 25mg 10mg 25mg

Fig. 9J

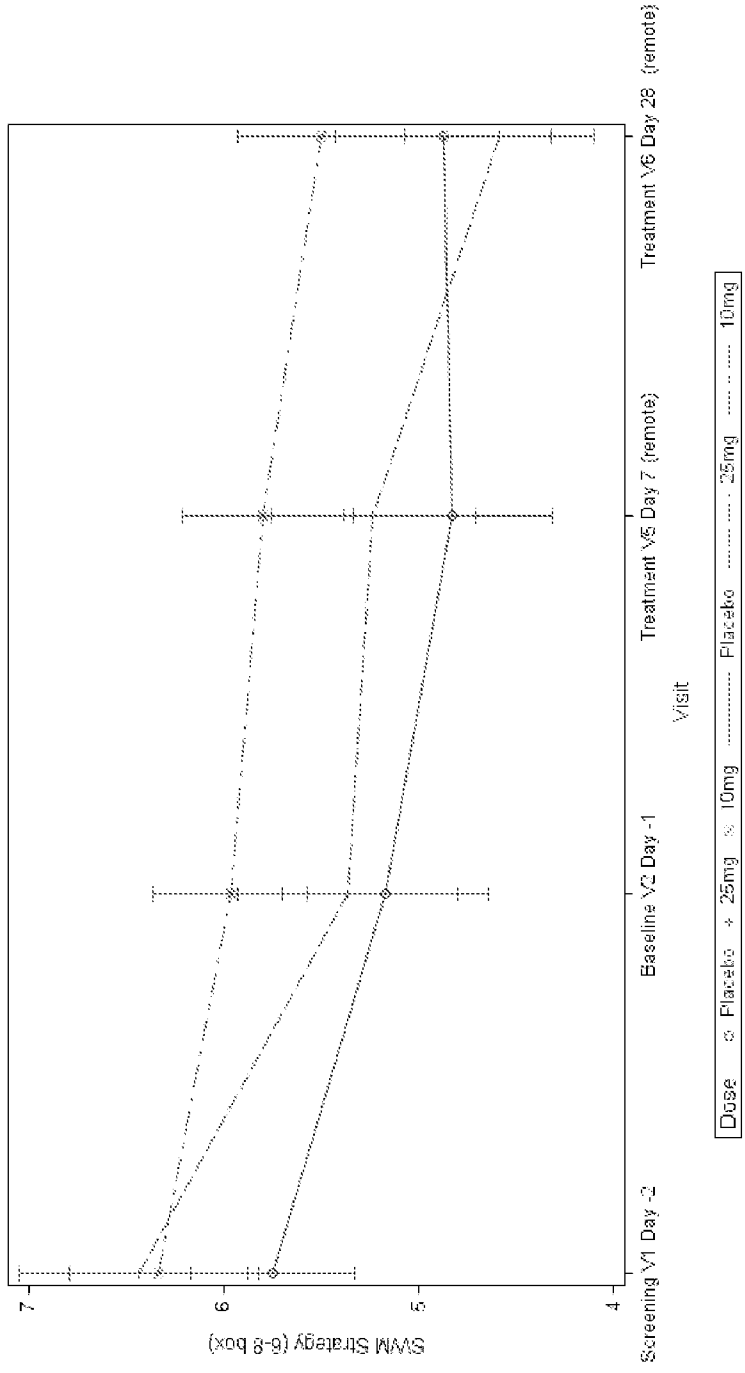

SWM Strategy (6-8 box)
7
6
5
4
Screening V1 Day -2
Baseline V2 Day -1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose
Placebo
25mg
10mg
Placebo
25mg
10mg

Fig. 9K

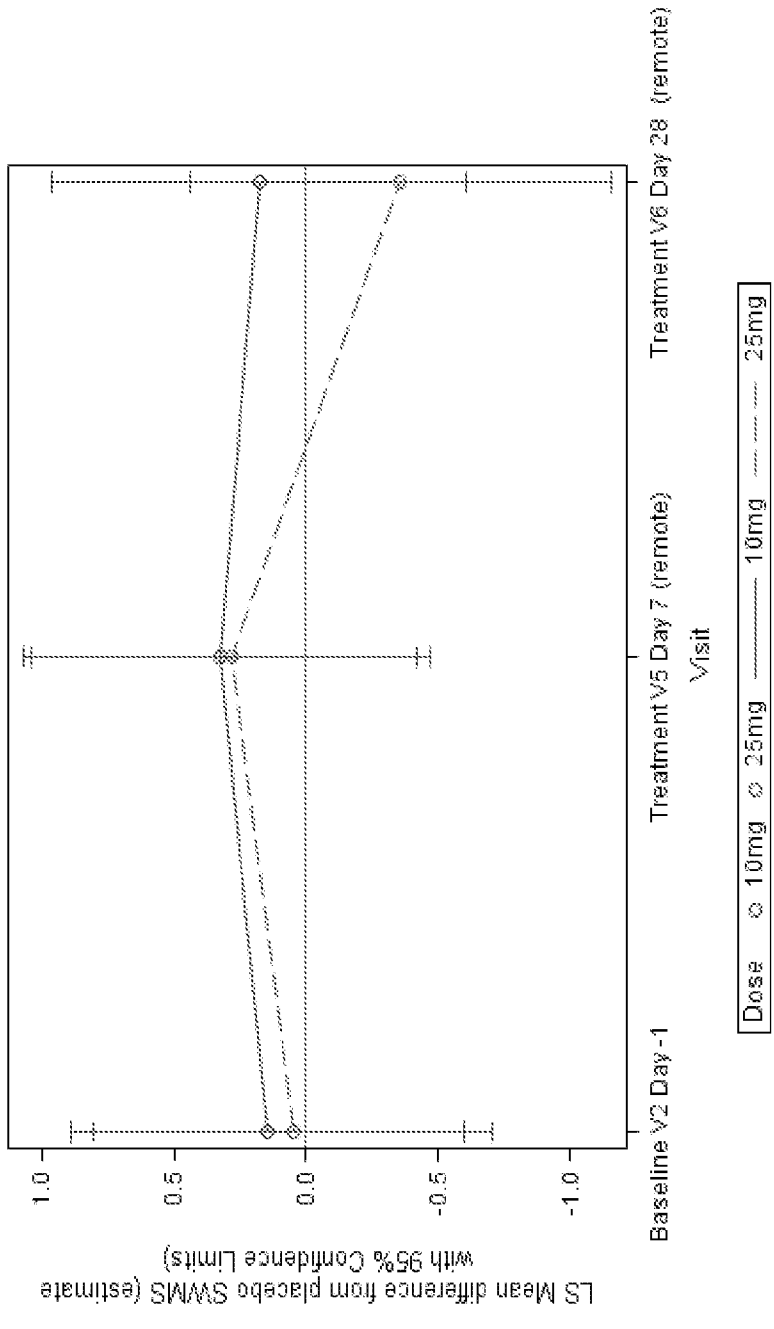
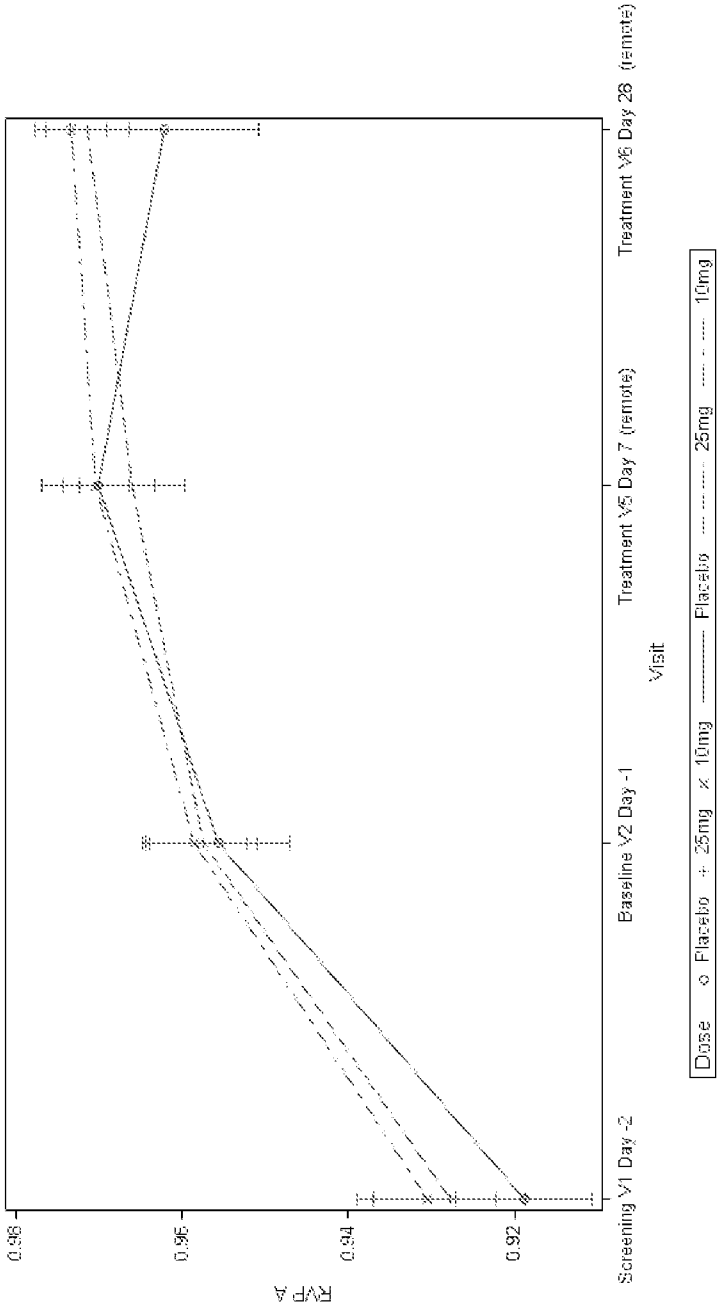

LS Mean difference from placebo SWMS (estimate with 95% Confidence Limits)
1.0
0.5
0.0
-0.5
-1.0
Baseline V2 Day -1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose
10mg
25mg
10mg
25mg

Fig. 9L


0.98
0.96
0.94
0.92
FEV1 A
Screening V1 Day -2
Baseline V2 Day -1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose
Placebo
25mg
10mg
Placebo
25mg
10mg

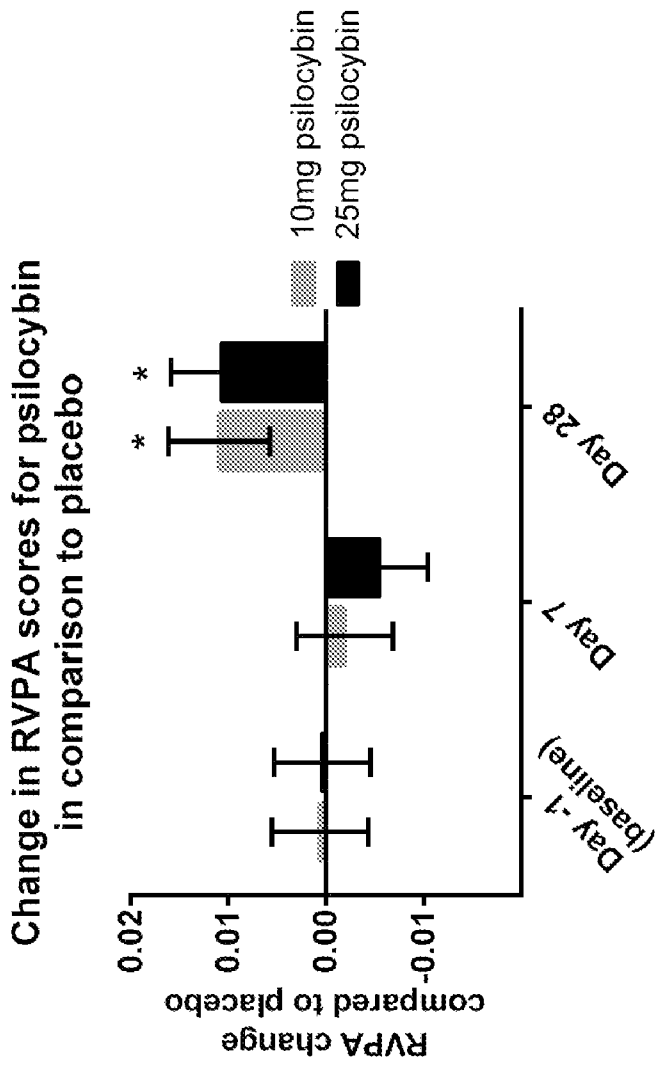

Change in RVPA scores for psilocybin in comparison to placebo
10mg psilocybin
25mg psilocybin
RVPA change compared to placebo
0.02
0.01
0.00
-0.01
*
*
Day -1 (baseline)
Day 7
Day 28

Fig. 9M

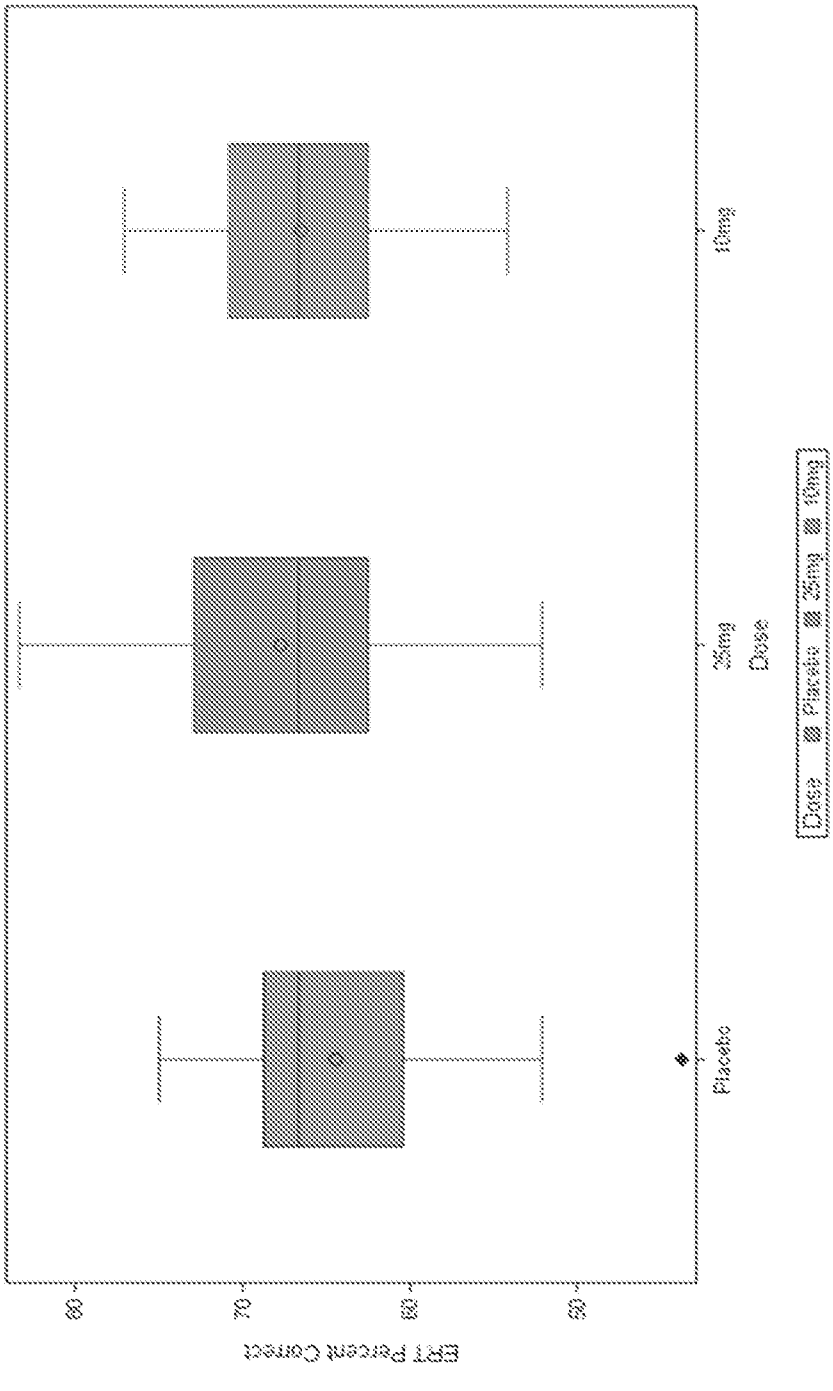

EBT Percent Correct
80
70
60
50
Placebo
2.5mg
10mg
Dose
Dose
Placebo
2.5mg
10mg

Fig. 9N

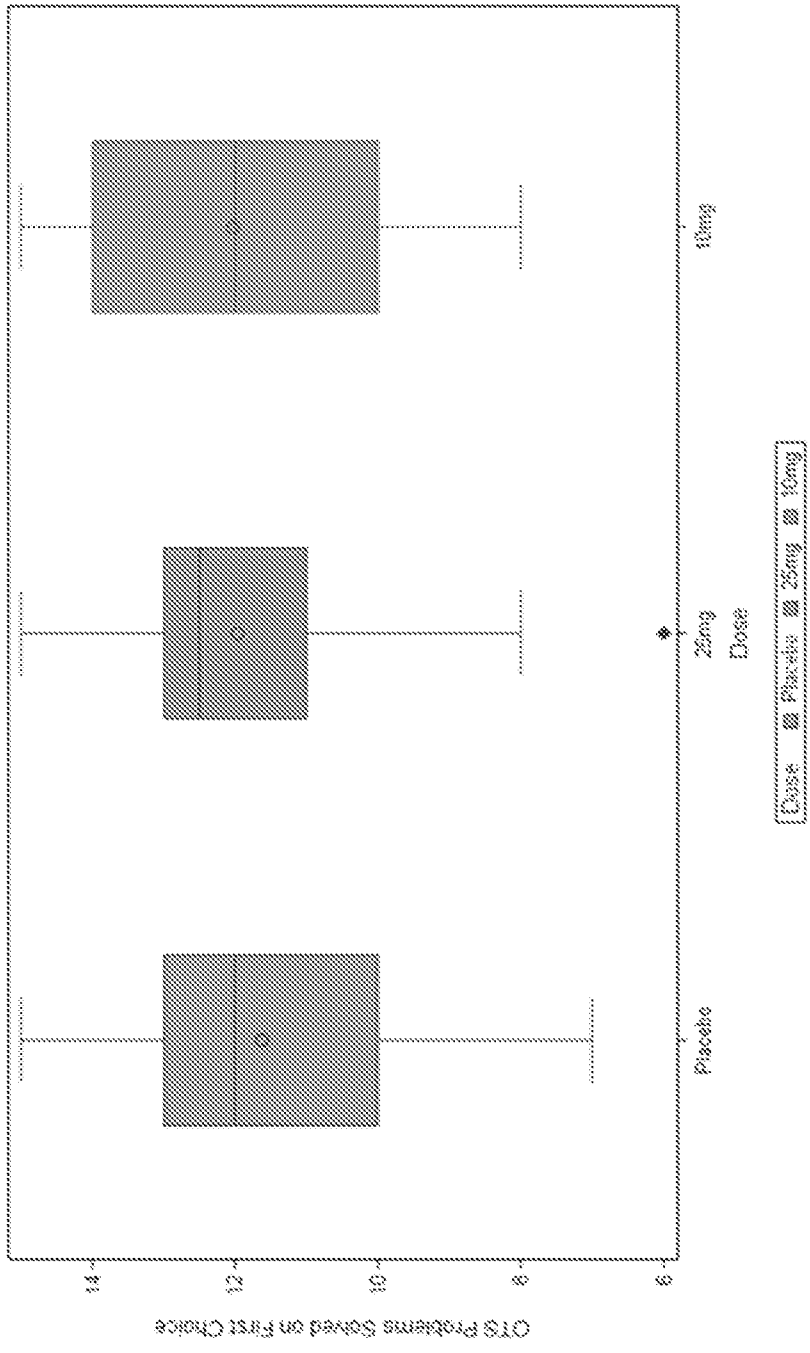

OTS Problems Solved on First Choice
14
12
10
8
6
Placebo
25mg
Dose
10mg
Dose
Placebo
25mg
10mg

Fig. 9O

Fig. 9P

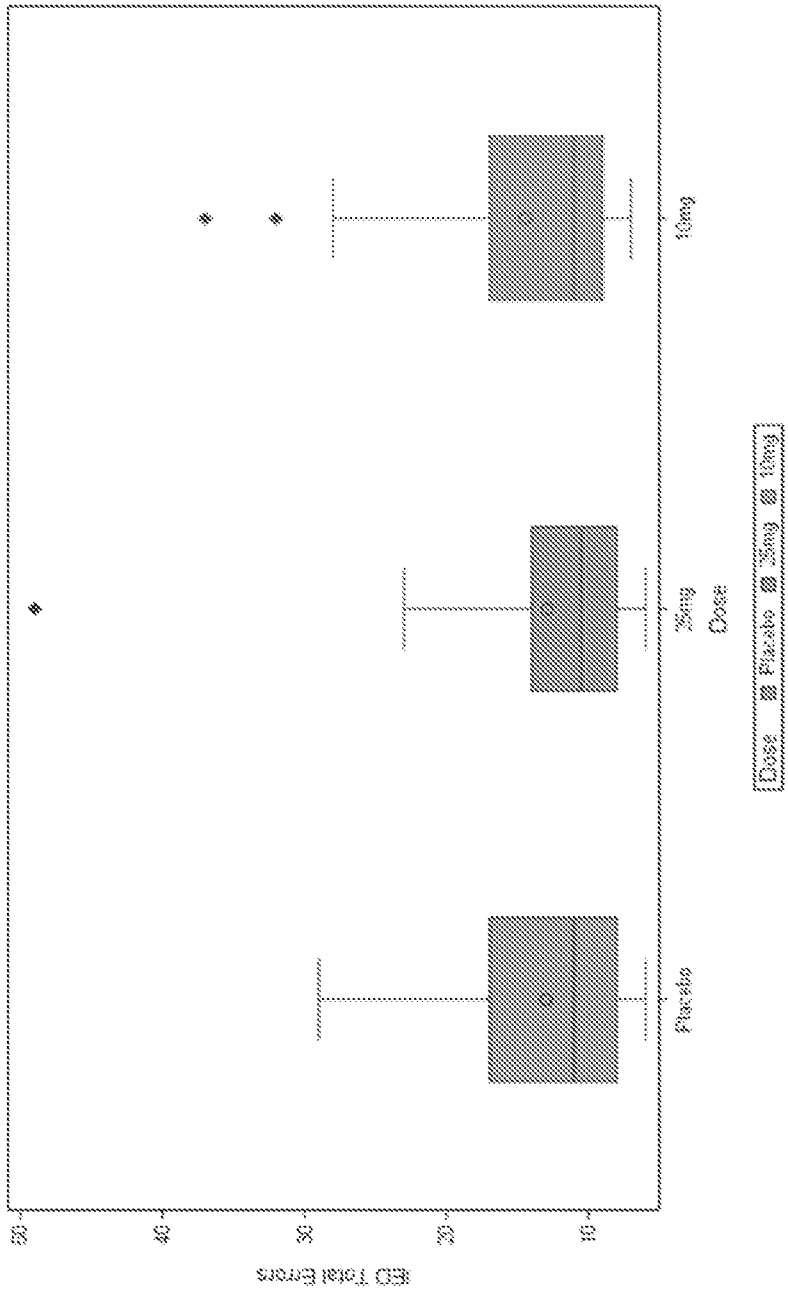


Fig. 9Q

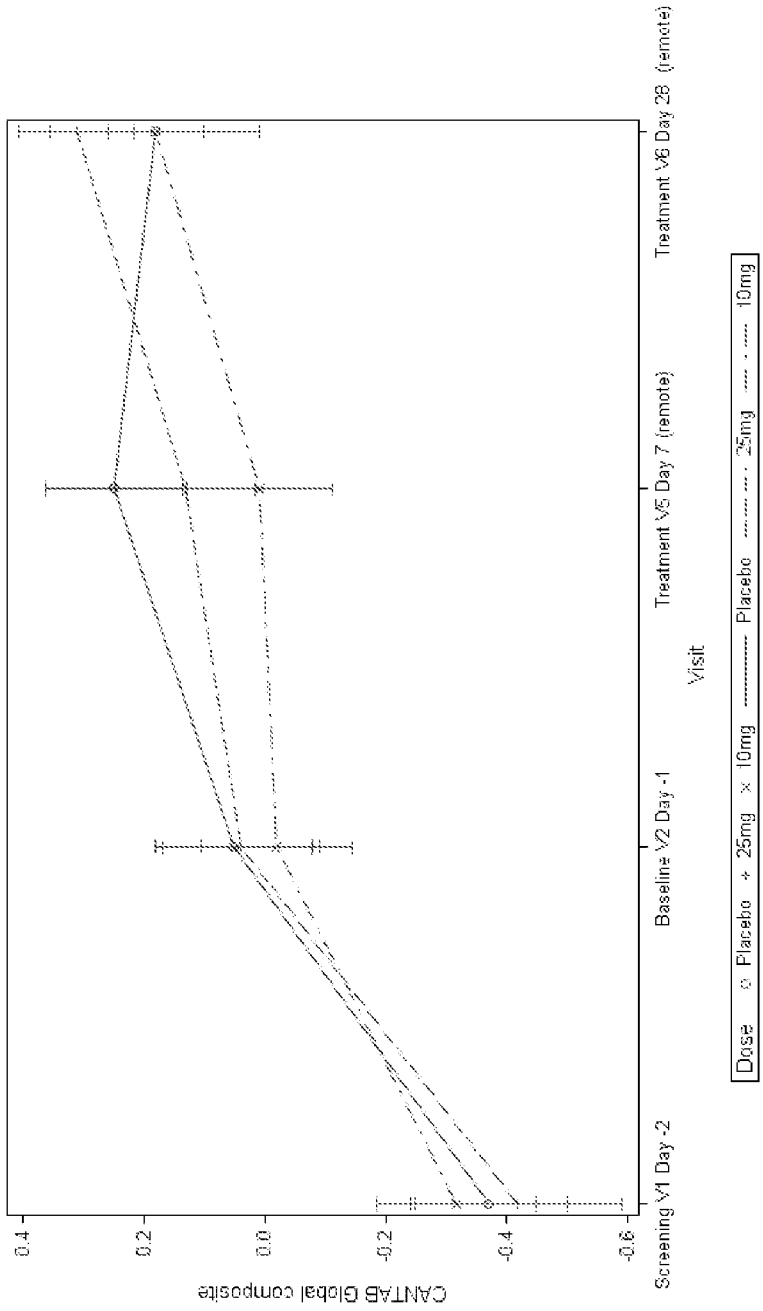

CANTAB Global composite
0.4
0.2
0.0
-0.2
-0.4
-0.6
Screening V1 Day -2
Baseline V2 Day -1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose Placebo 25mg 10mg Placebo 25mg 10mg

Fig. 9R

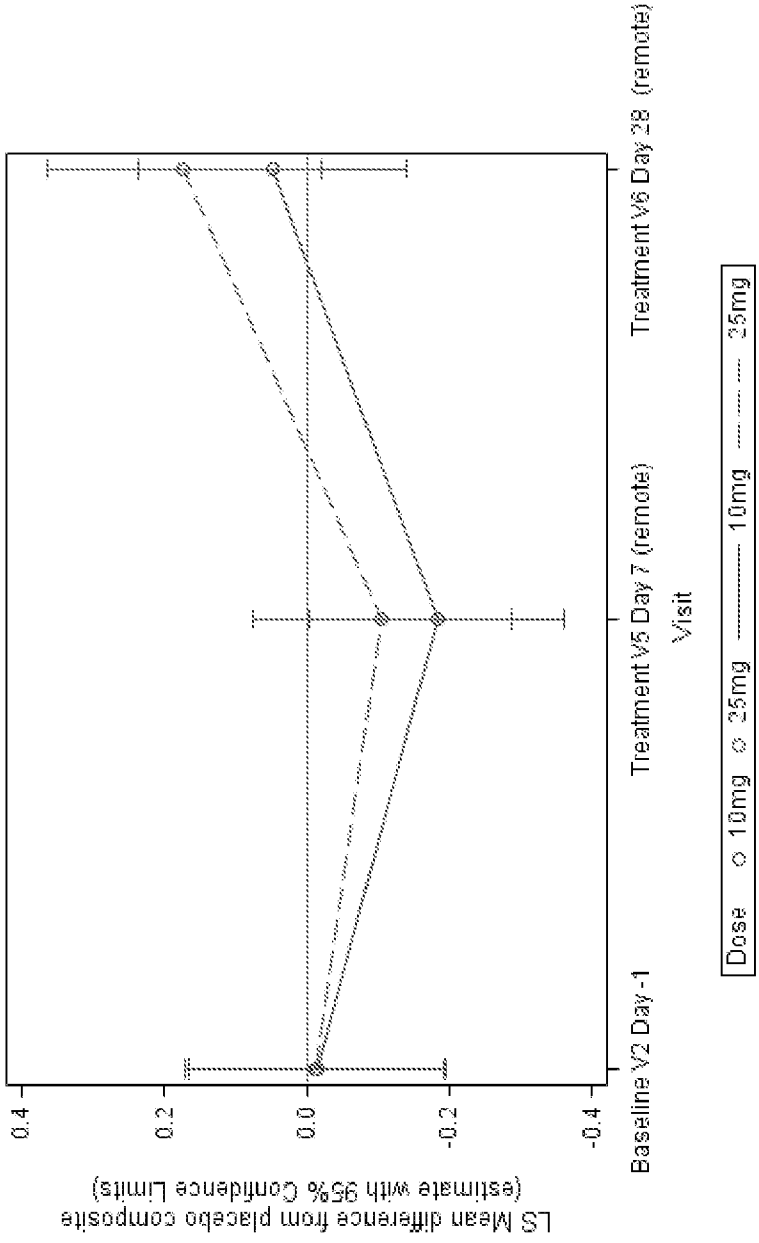

LS Mean difference from placebo composite
(estimate with 95% Confidence Limits)
0.4
0.2
0.0
-0.2
-0.4
Baseline V2 Day -1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose 10mg 25mg 10mg 25mg

Fig. 9S

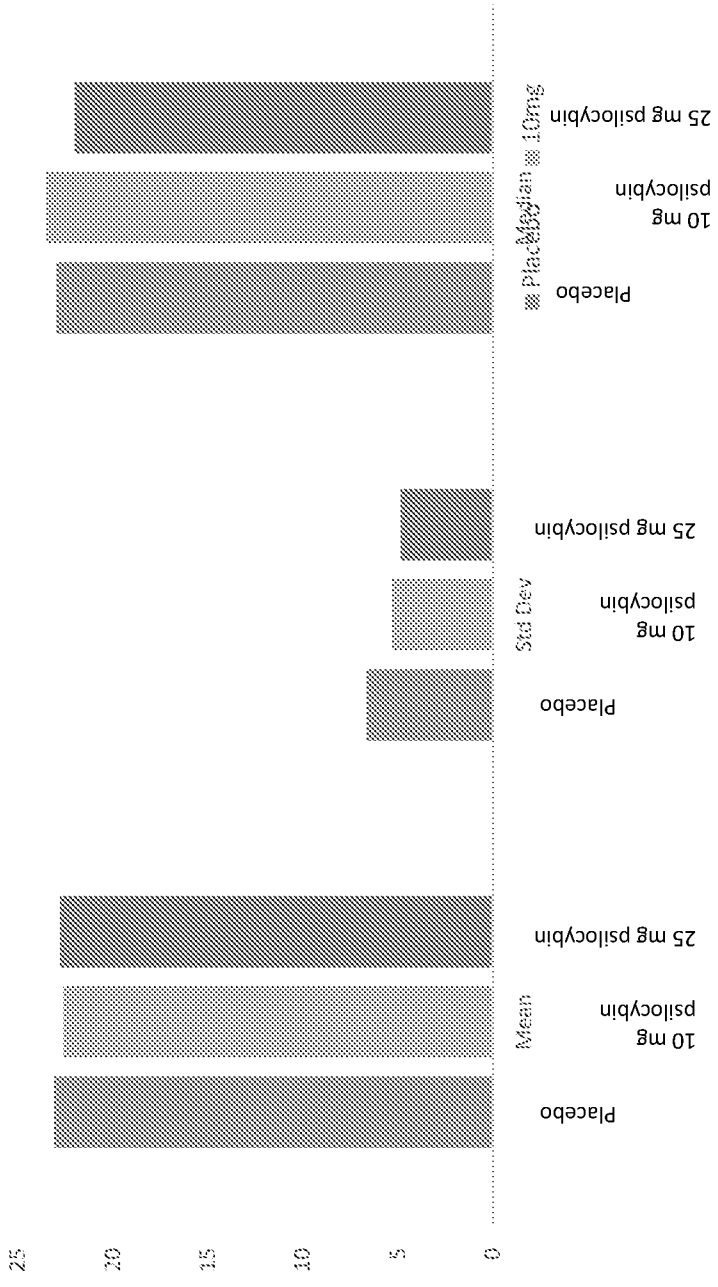
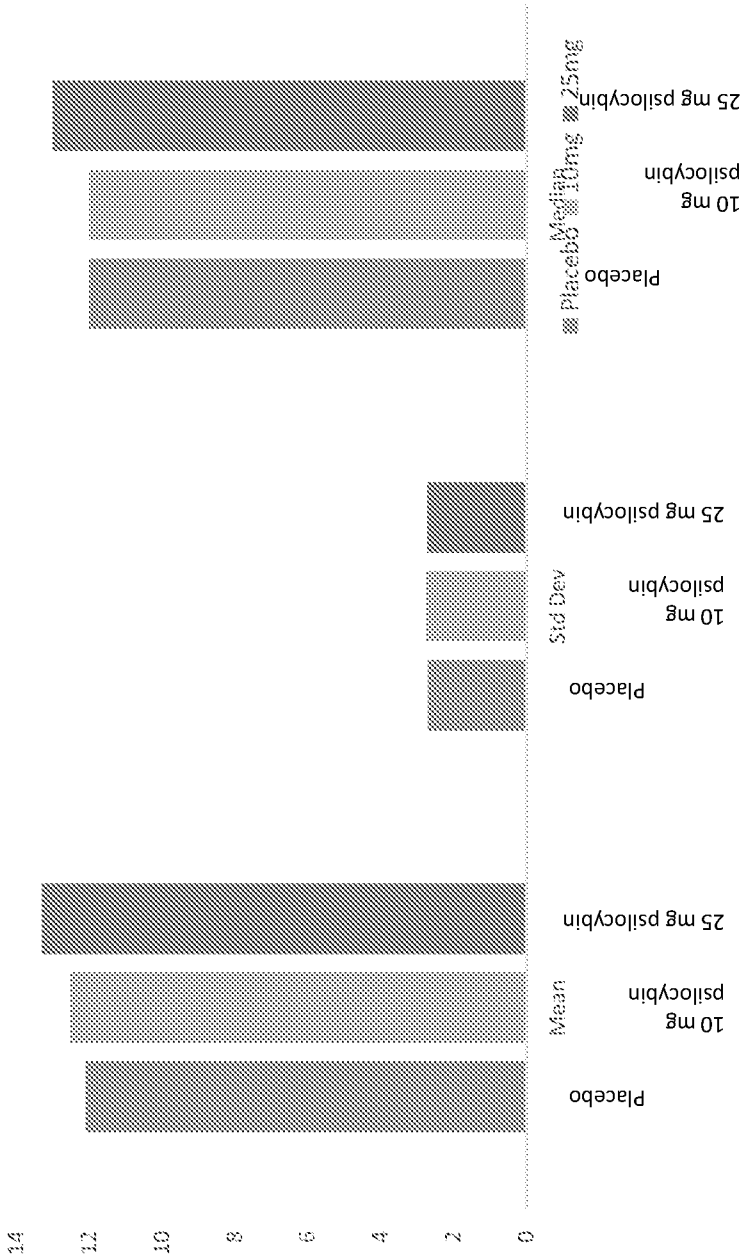

25
20
15
10
5
0
Mean
Placebo
10 mg psilocybin
25 mg psilocybin
Std Dev
Placebo
10 mg psilocybin
25 mg psilocybin
Median
Placebo
10 mg psilocybin
25 mg psilocybin

Fig. 9T


14
12
10
8
6
4
2
0
Mean
Placebo
10 mg psilocybin
25 mg psilocybin
Std Dev
Placebo
10 mg psilocybin
25 mg psilocybin
Median
Placebo
10 mg psilocybin
25 mg psilocybin

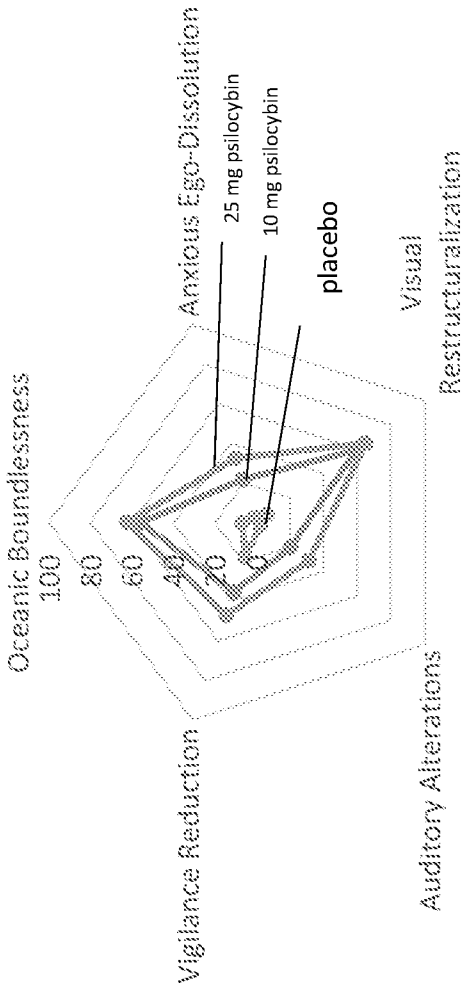

Oceanic Boundlessness
100
80
60
40
20
0
Anxious Ego-Dissolution
Visual Restructuralization
Auditory Alterations
Vigilance Reduction
25 mg psilocybin
10 mg psilocybin
placebo

Fig. 9U

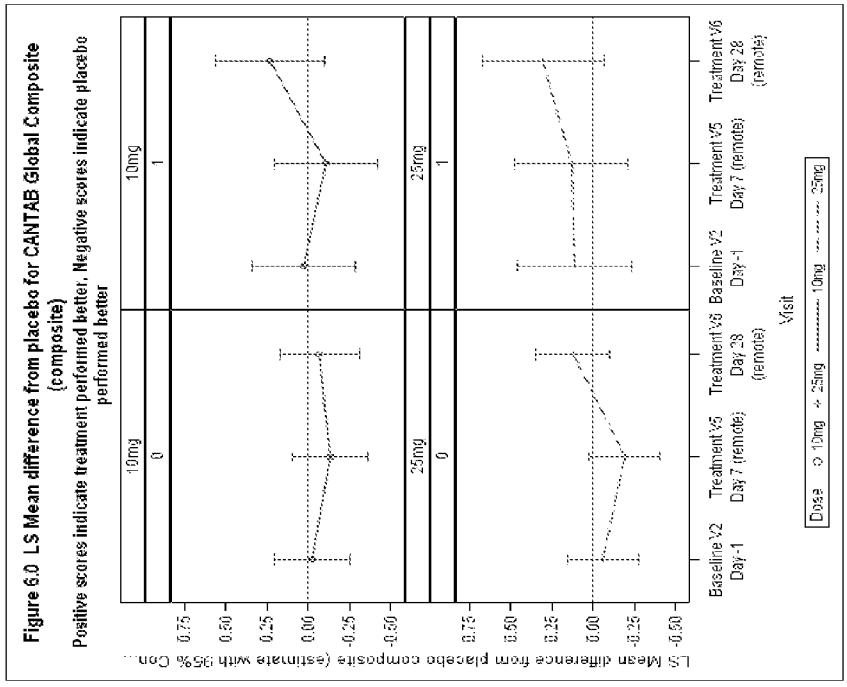

Figure 6.0 LS Mean difference from placebo for CANTAB Global Composite (composite)
Positive scores indicate treatment performed better, Negative scores indicate placebo performed better
10mg
0
1
25mg
LS Mean difference from placebo composite (estimate with 95% Con...
0.75
0.50
0.25
0.00
-0.25
-0.50
Baseline V2 Day-1
Treatment V5 Day 7 (remote)
Treatment V6 Day 28 (remote)
Visit
Dose 10mg 25mg 10mg 25mg

Fig. 9V

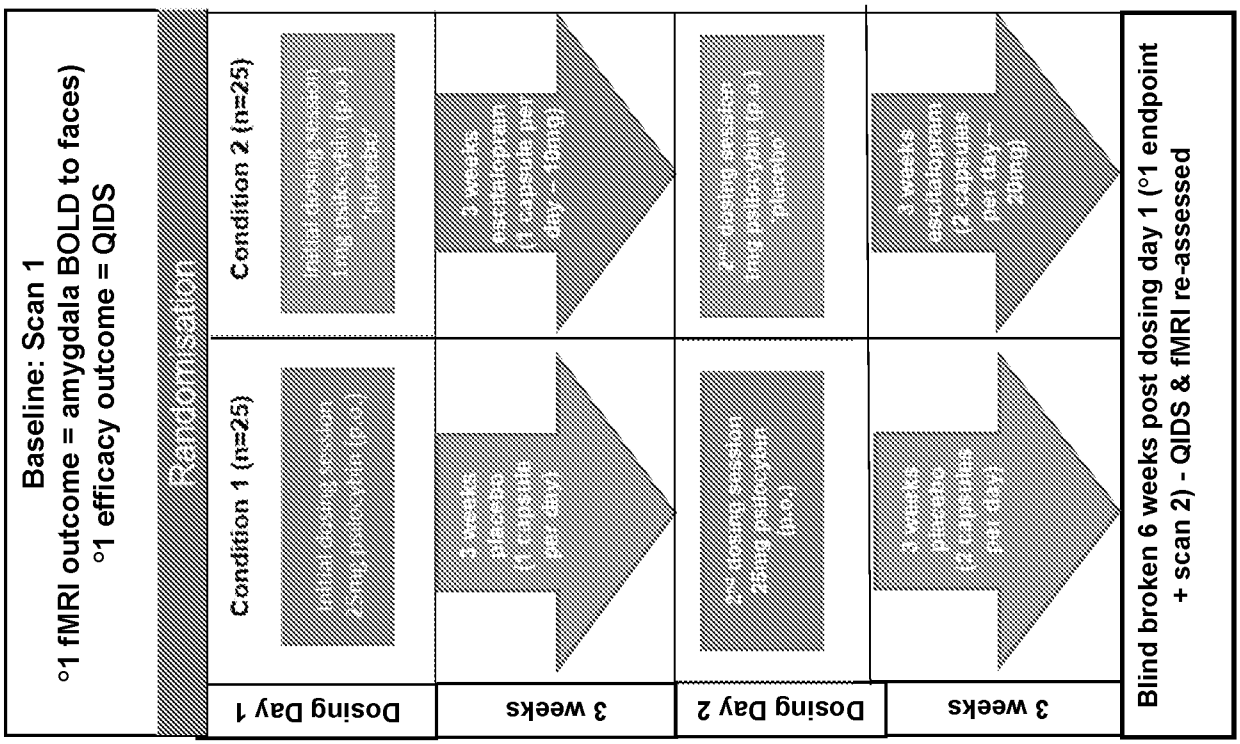

Baseline: Scan 1
°1 fMRI outcome = amygdala BOLD to faces)
°1 efficacy outcome = QIDS
Randomisation
Condition 1 (n=25)
Condition 2 (n=25)
Dosing Day 1
3 weeks
Dosing Day 2
3 weeks
Blind broken 6 weeks post dosing day 1 (°1 endpoint
+ scan 2) - QIDS & fMRI re-assessed

Fig. 10A

Fig. 10B

Study Timeline			
Date	**Event**	**Main assessment/s**	**Approximate Duration**
Visit 1	Screening	QIDS, HAM-D MADRS, ECG	5 hours
Visit 2	Scan 1	QIDS, HAM-D, MADRS, scan measures	5 hours
Visit 3	Dosing session 1 (DS1)	ASC, EDI, etc	8 hours
Visit 4	1-day post DS1	QIDS, interview	2-3 hours
Visit 5	Dosing session 2 (DS2)	ASC, EDI, etc	8 hours
Visit 6	1 day post DS2	QIDS, interview	2-3 hours
Visit 7	Final visit + scan 2 6-weeks post DS1	QIDS, HAM-D, MADRS interview, ECG, scan measures	5 hours

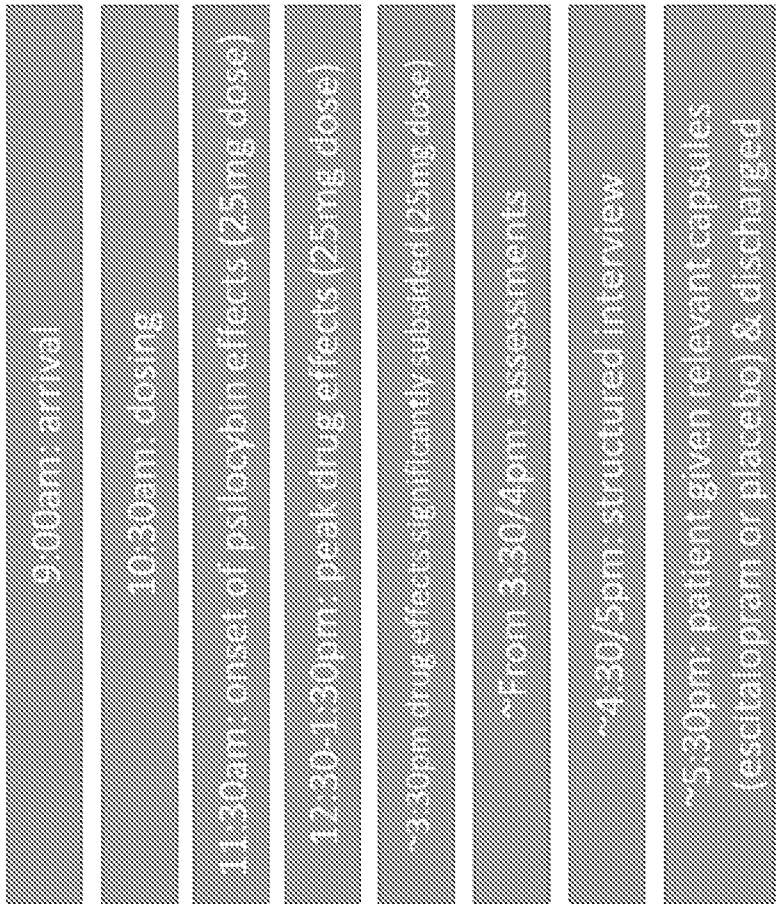
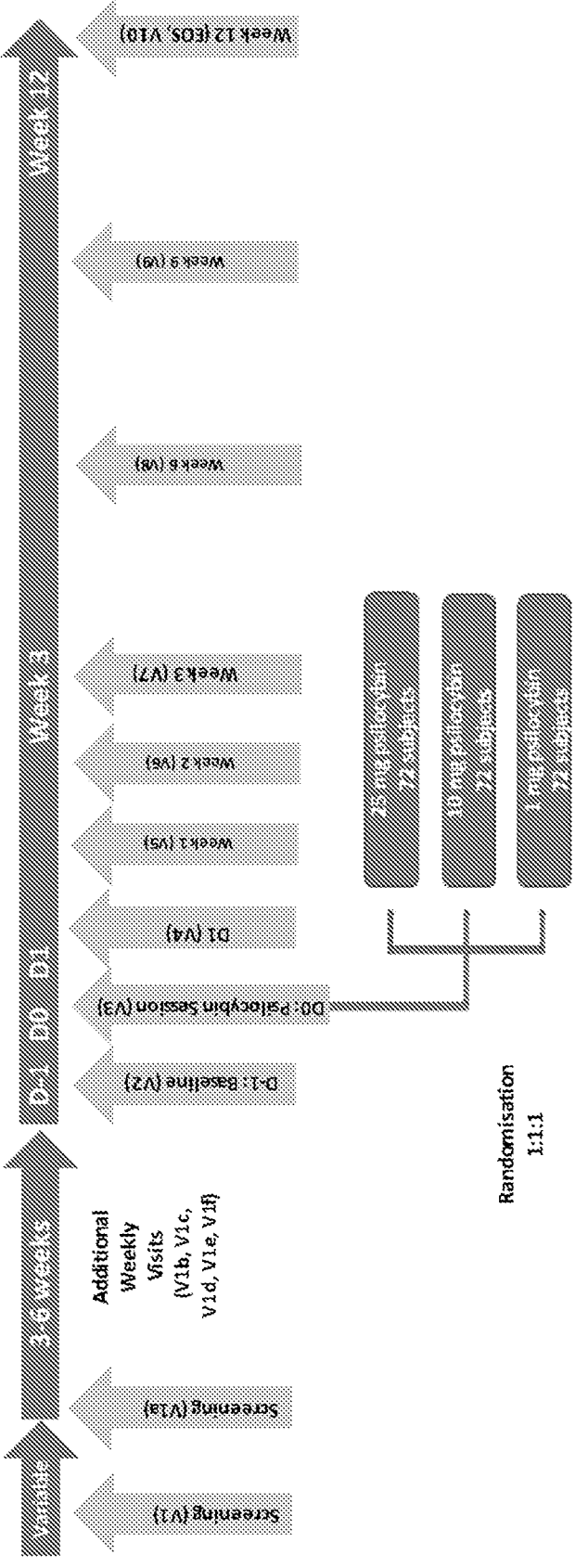

9:00am: arrival
10:30am: dosing
11:30am: onset of psilocybin effects (25mg dose)
12:30-1:30pm: peak drug effects (25mg dose)
~3:30pm: drug effects equilibrated/subsided (25mg dose)
~4-10pm: 3:30/4pm assessments
~4:30/5pm: structured interview
~5:30pm: patient given relevant capsules
(escitalopram or placebo) & discharged

Fig. 10C

Fig. 11



Abbreviations: D = day; EoS = End of Study; V = Visit

Fig. 12

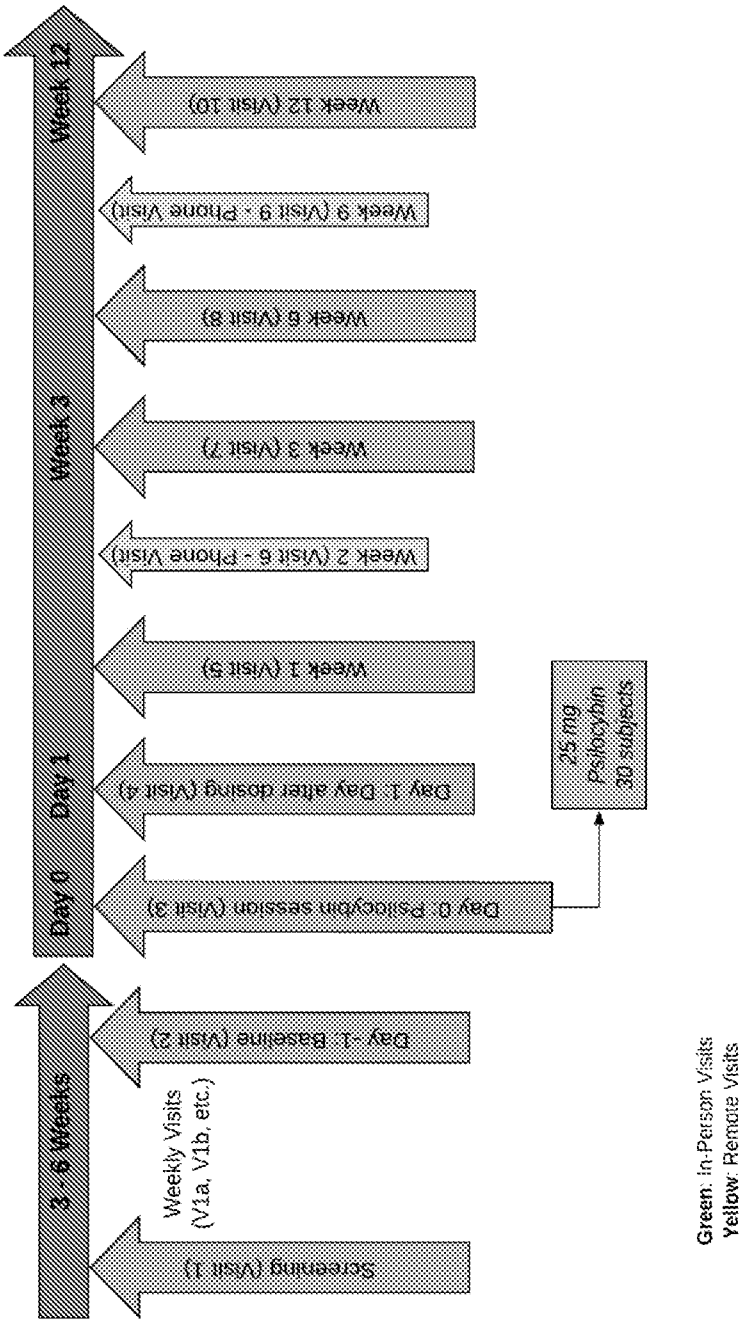
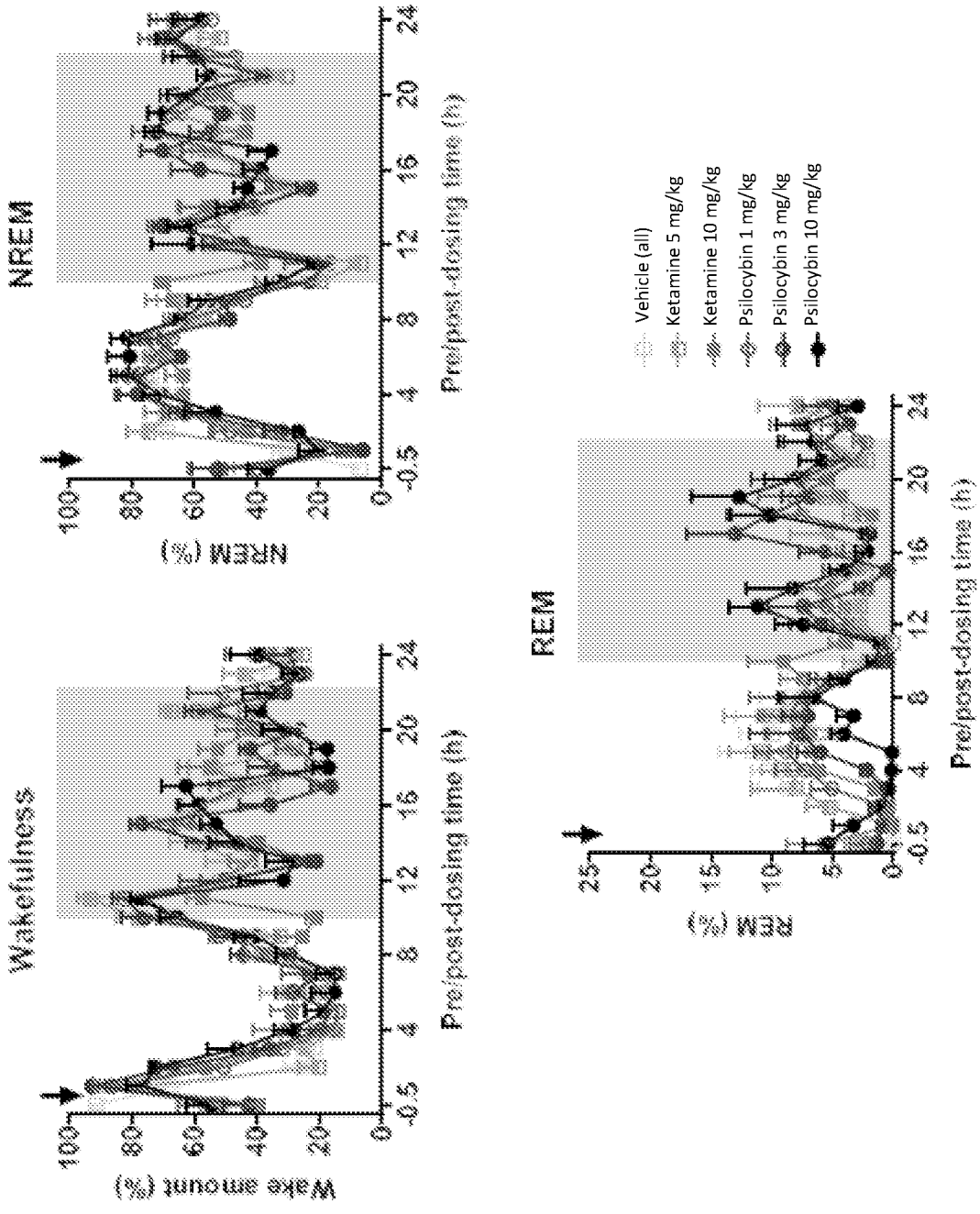

Screening (Visit 1)
Weekly Visits
(V1a, V1b, etc.)
Day -1: Baseline (Visit 2)
Day 0: Psilocybin session (Visit 3)
25 mg
Psilocybin
30 subjects
Day 1: Day after dosing (Visit 4)
Week 1 (Visit 5)
Week 2 (Visit 6 - Phone Visit)
Week 3 (Visit 7)
Week 6 (Visit 8)
Week 9 (Visit 9 - Phone Visit)
Week 12 (Visit 10)
3 - 6 Weeks
Day 0
Day 1
Week 3
Week 12
Green: In-Person Visits
Yellow: Remote Visits

Fig. 13A


Wakefulness
Wake amount (%)
Pre/post-dosing time (h)
NREM
NREM (%)
Pre/post-dosing time (h)
REM
REM (%)
Pre/post-dosing time (h)
Vehicle (all)
Ketamine 5 mg/kg
Ketamine 10 mg/kg
Psilocybin 1 mg/kg
Psilocybin 3 mg/kg
Psilocybin 10 mg/kg

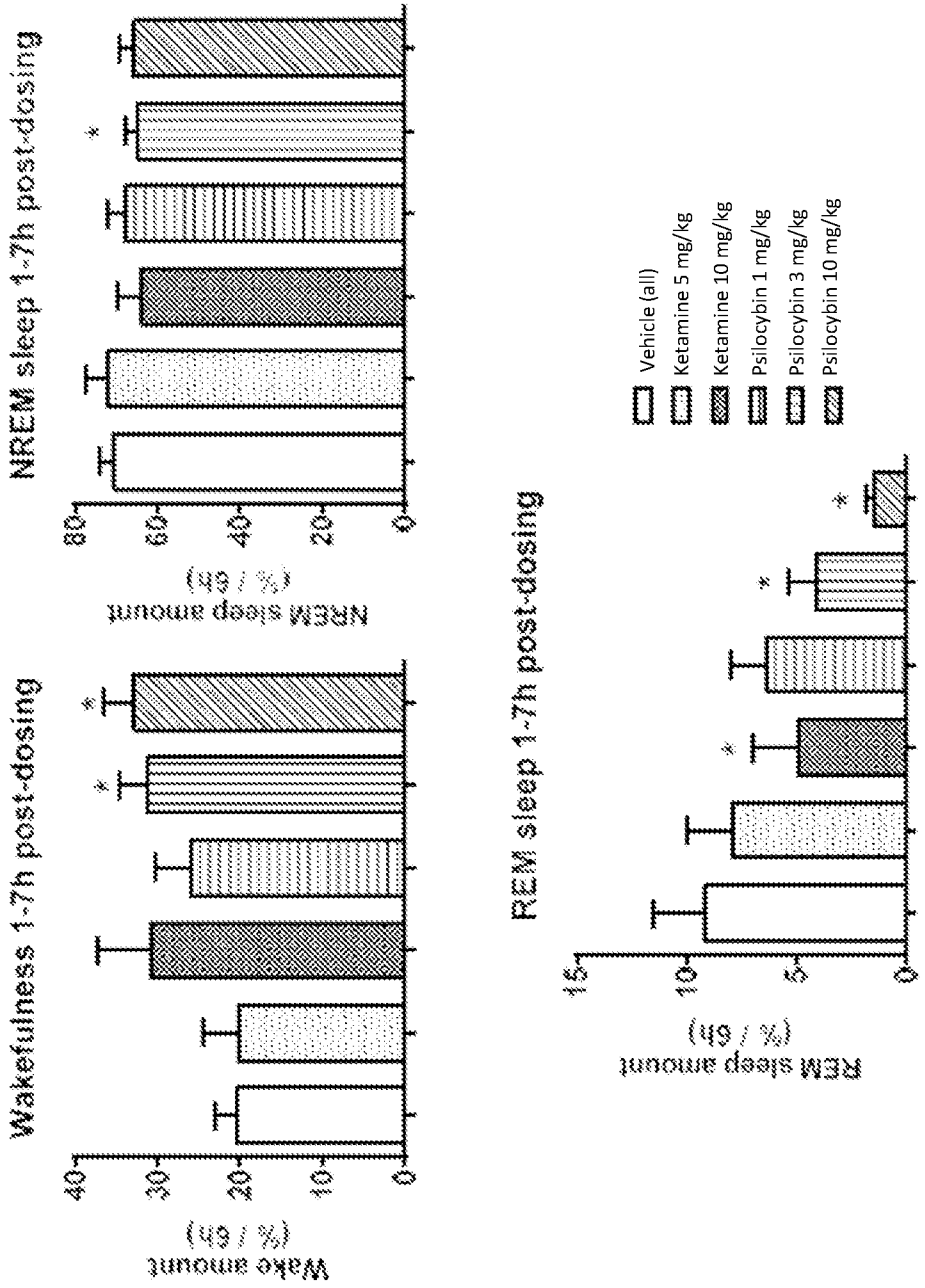

Wakefulness 1-7h post-dosing
Wake amount (% / 6h)
40
30
20
10
0
*
*
NREM sleep 1-7h post-dosing
NREM sleep amount (% / 6h)
80
60
40
20
0
*
REM sleep 1-7h post-dosing
REM sleep amount (% / 6h)
15
10
5
0
*
*
*
Vehicle (all)
Ketamine 5 mg/kg
Ketamine 10 mg/kg
Psilocybin 1 mg/kg
Psilocybin 3 mg/kg
Psilocybin 10 mg/kg

Fig. 13B

Fig. 13C

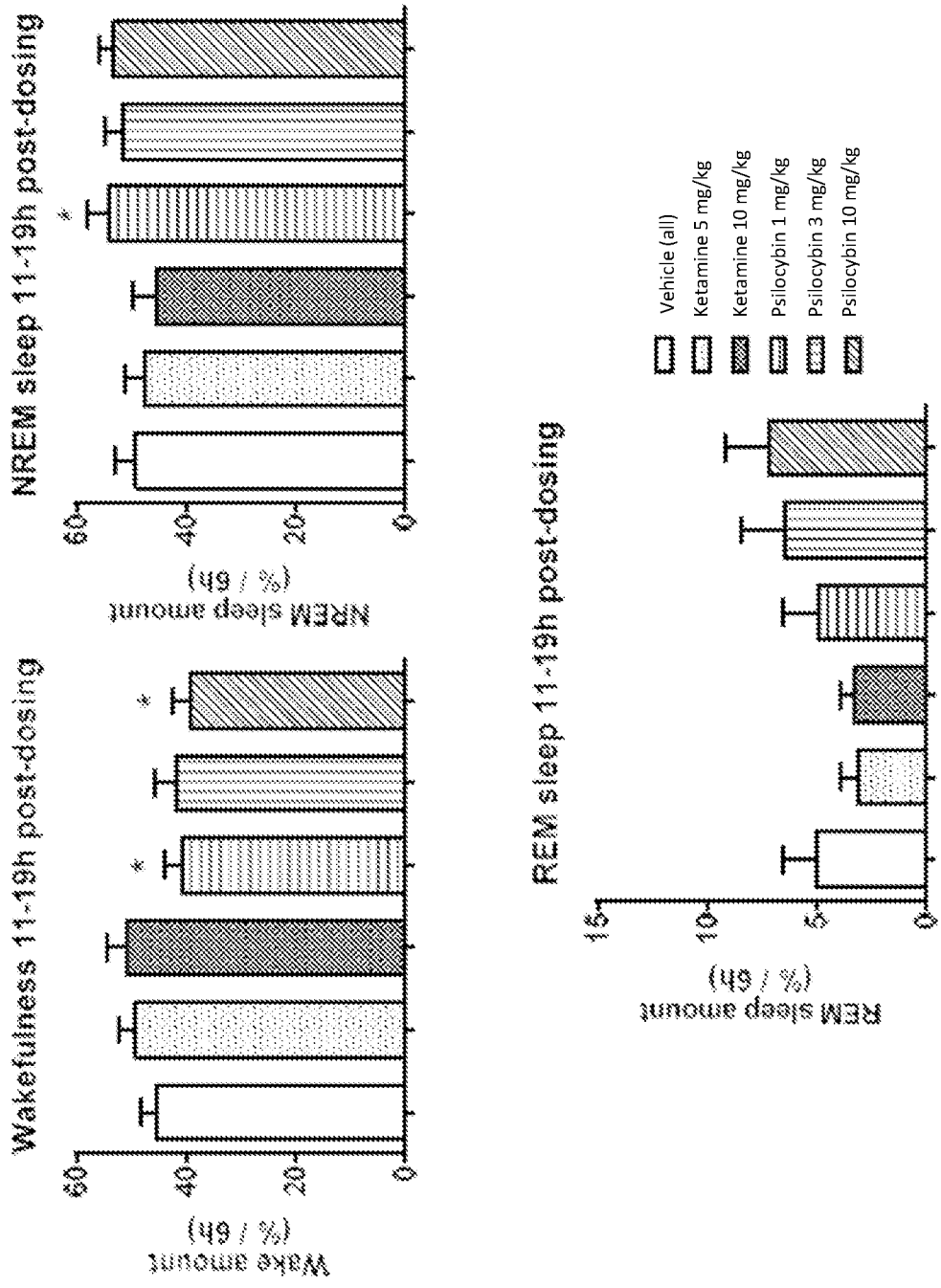
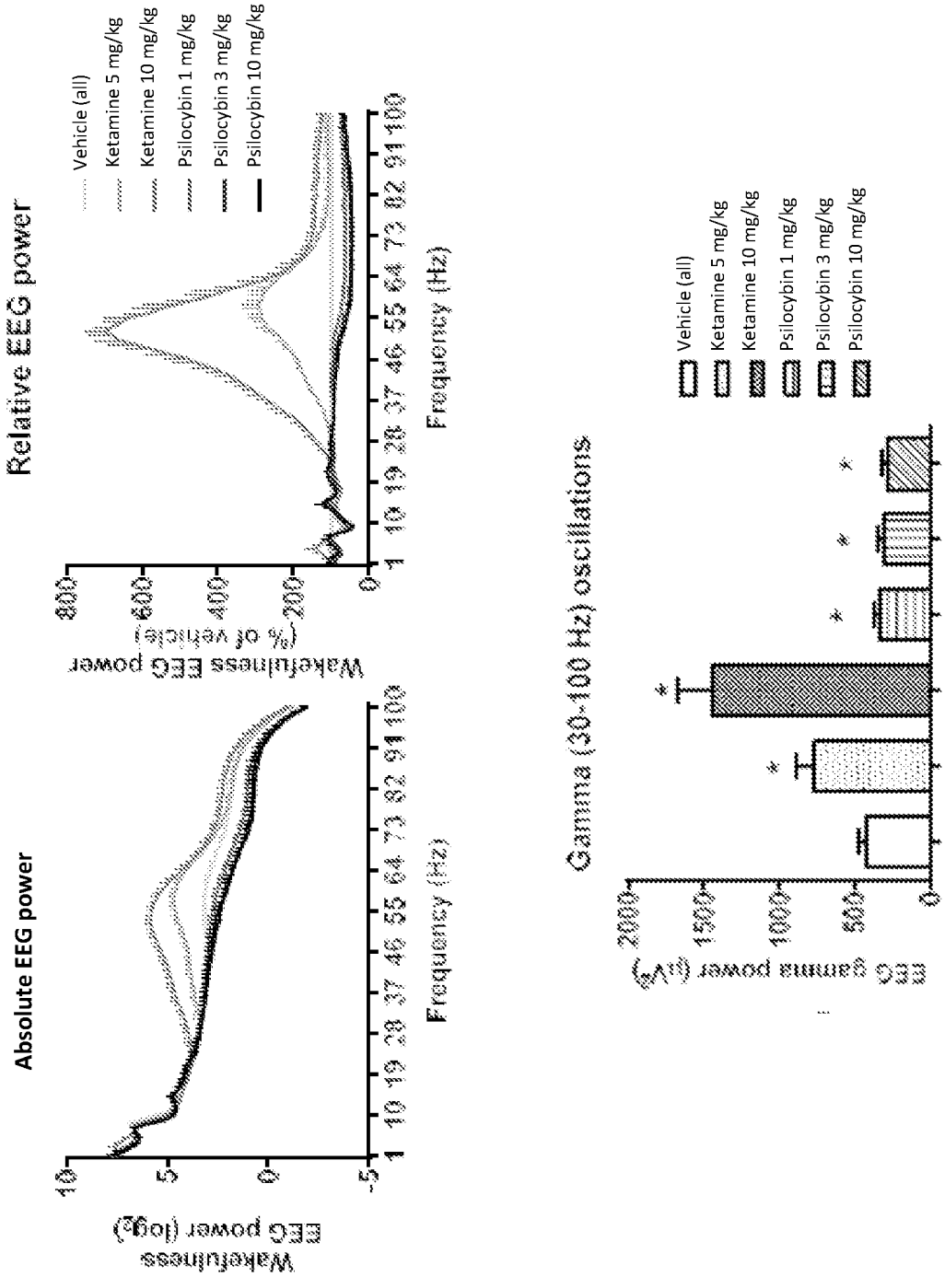

Wakefulness 11-19h post-dosing
Wake amount (% / 6h)
60
40
20
0
*
*
NREM sleep 11-19h post-dosing
NREM sleep amount (% / 6h)
60
40
20
0
*
REM sleep 11-19h post-dosing
REM sleep amount (% / 6h)
15
10
5
0
Vehicle (all)
Ketamine 5 mg/kg
Ketamine 10 mg/kg
Psilocybin 1 mg/kg
Psilocybin 3 mg/kg
Psilocybin 10 mg/kg

Fig. 13D


Absolute EEG power
Wakefulness EEG power (log10)
Frequency (Hz)
Relative EEG power
Wakefulness EEG power (% of vehicle)
Frequency (Hz)
Vehicle (all)
Ketamine 5 mg/kg
Ketamine 10 mg/kg
Psilocybin 1 mg/kg
Psilocybin 3 mg/kg
Psilocybin 10 mg/kg
Gamma (30-100 Hz) oscillations
EEG gamma power (μV²)

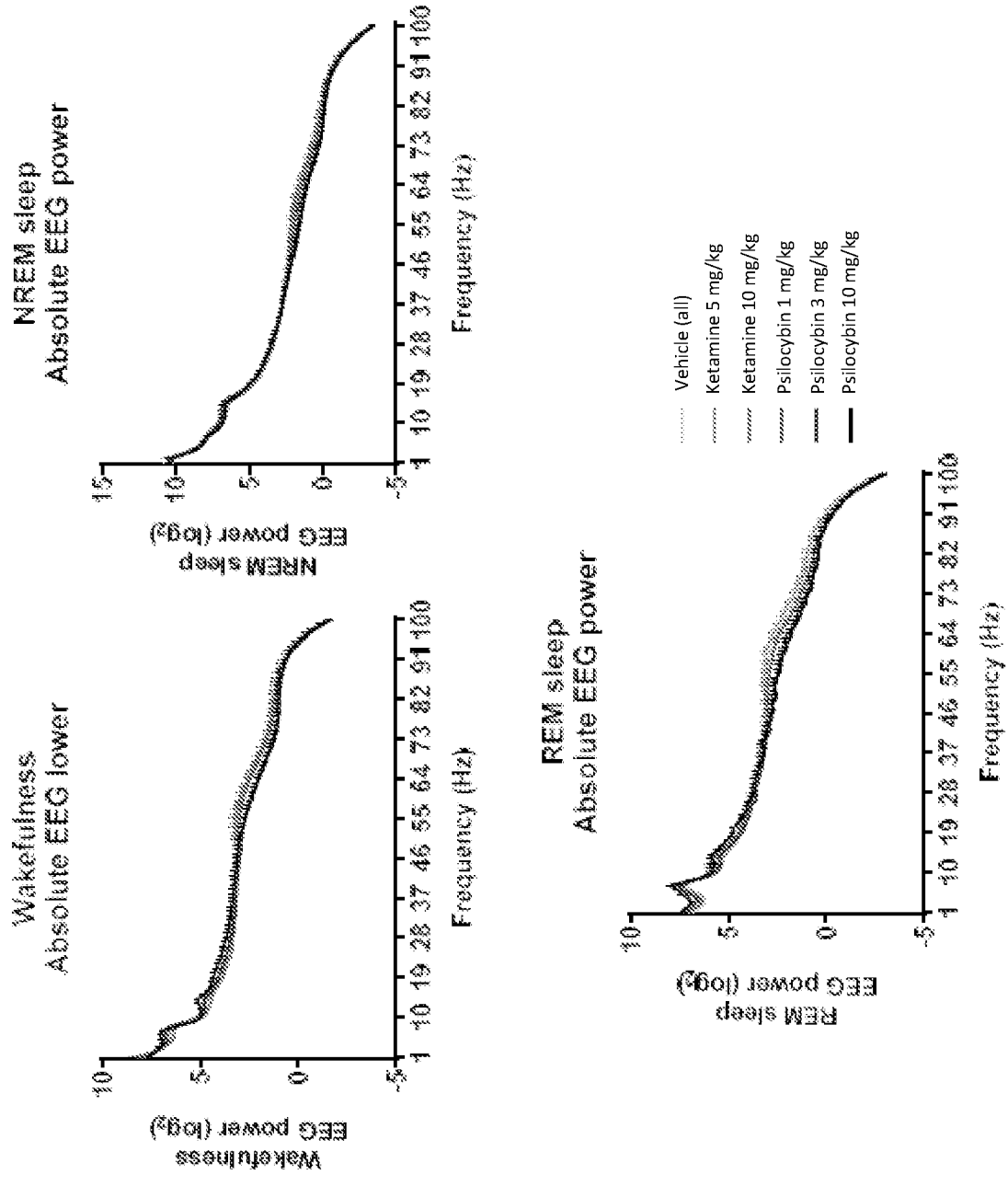
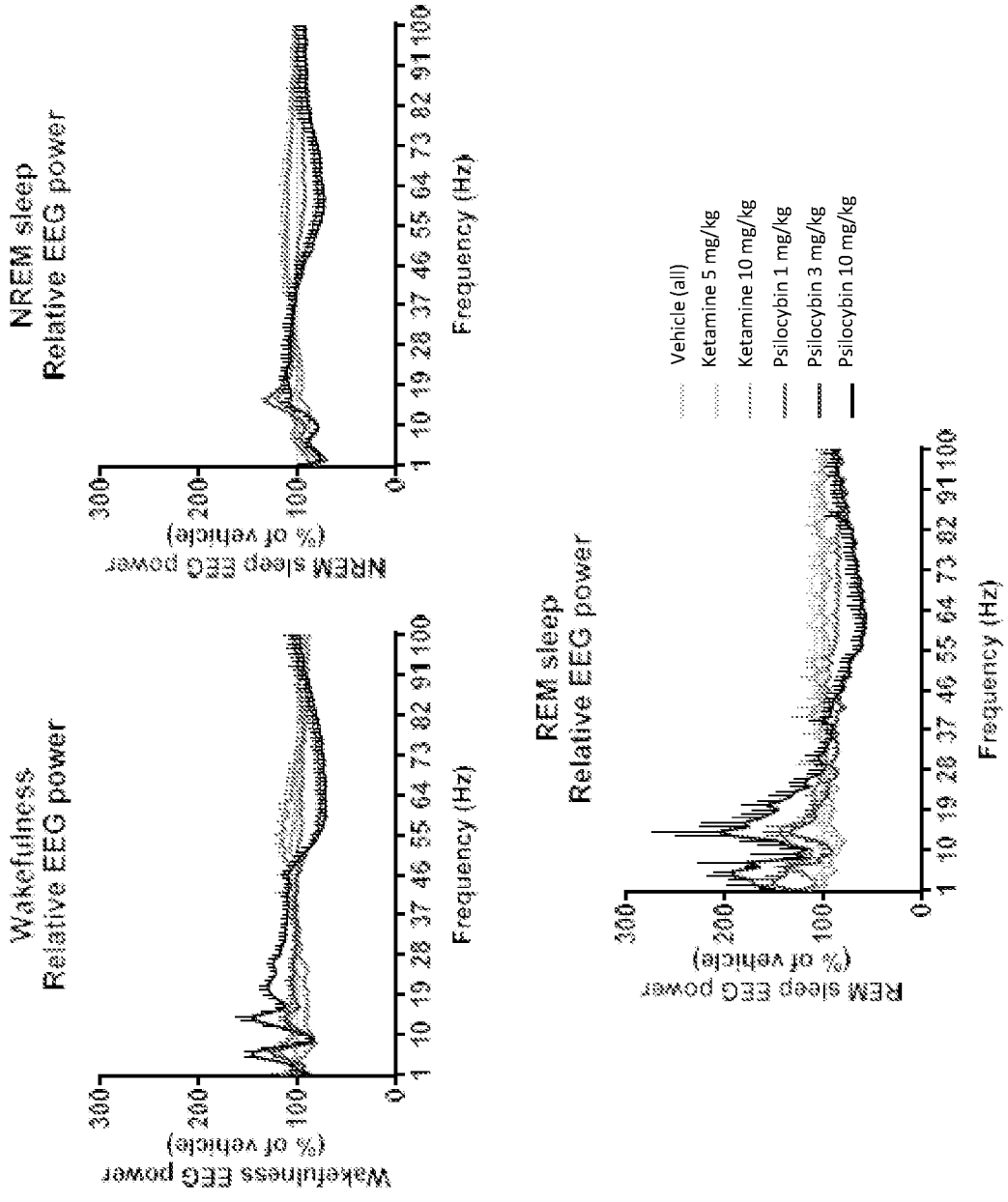

Wakefulness
Absolute EEG power
Wakefulness
EEG power (log2)
Frequency (Hz)
NREM sleep
Absolute EEG power
NREM sleep
EEG power (log2)
Frequency (Hz)
REM sleep
Absolute EEG power
REM sleep
EEG power (log2)
Frequency (Hz)
Vehicle (all)
Ketamine 5 mg/kg
Ketamine 10 mg/kg
Psilocybin 1 mg/kg
Psilocybin 3 mg/kg
Psilocybin 10 mg/kg

Fig. 13E

Fig. 13E (continued)



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/053688

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/675 A61K31/4045 A61P1/00 A61P25/16 A61P25/30
A61P25/00 A61P25/06 A61P25/22
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R L CARHART-HARRIS ET AL: "Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study", LANCET PSYCHIATRY, vol. 3, no. 7, 17 May 2016 (2016-05-17), pages 619-627, XP055708476, the whole document ----- -/--	1-3, 7-12, 16-18, 20,21, 32,33, 59,60, 62-65, 67,74, 76-80, 82-84, 86-92, 94,98, 101, 103-105, 111, 126-129, 142-144

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2020	26/08/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Allnutt, Sarah

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CARHART-HARRIS R L ET AL: "Psilocybin with psychological support for treatment-resistant depression: six-month follow-up", PSYCHOPHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 235, no. 2, 8 November 2017 (2017-11-08), pages 399-408, XP036415992, ISSN: 0033-3158, DOI: 10.1007/S00213-017-4771-X [retrieved on 2017-11-08] the whole document ----- WO 2018/135943 A1 (PROCARE BEHEER B V) 26 July 2018 (2018-07-26) claims 1,2; example 1 ----- WO 2018/148605 A1 (CAAMTECH LLC [US]) 16 August 2018 (2018-08-16) page 51, paragraph 5; claims 102,121-124 ----- KAELEN MENDEL ET AL: "The hidden therapist: evidence for a central role of music in psychedelic therapy", PSYCHOPHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 235, no. 2, 2 February 2018 (2018-02-02), pages 505-519, XP036416002, ISSN: 0033-3158, DOI: 10.1007/S00213-017-4820-5 [retrieved on 2018-02-02] page 506, column 1, paragraph 3 - page 507, column 2, paragraph 1; figures 3,4 page 515, column 2, paragraph 3 See Abstract and conclusion; page 516, lines 34-37 ----- -/--	1-3, 7-12, 16-18, 20,26, 32,33, 59,60, 62-65, 67,74, 76-79, 111, 126-129, 142-144 1-6,8,9, 20,32, 33,59, 60, 63-68, 74, 77-79, 111,117, 128,129 1-4,8,9, 21,22, 32,33, 59,64, 65,78, 79, 127-129, 139 1-3, 7-11,21, 25-27, 32,33, 59,60, 62-65, 67,74, 76-80, 82-84, 86-94, 111, 126-129

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/053688

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATRA SURAVI: "Return of the psychedelics: Psilocybin for treatment resistant depression", ASIAN JOURNAL OF PSYCHIATRY, ELSEVIER, AMSTERDAM, NL, vol. 24, 23 August 2016 (2016-08-23), pages 51-52, XP029832871, ISSN: 1876-2018, DOI: 10.1016/J.AJP.2016.08.010 the whole document --- BAS T.H. DE VEEN ET AL: "Psilocybin for treating substance use disorders?", EXPERT REVIEW OF NEUROTHERAPEUTICS, vol. 17, no. 2, 12 August 2016 (2016-08-12), pages 203-212, XP055707549, GB ISSN: 1473-7175, DOI: 10.1080/14737175.2016.1220834 Section 2.2; Section 3 --- ANDREW SEWELL R ET AL: "Response of cluster headache to psilocybin and LSD", NEUROLOGY, LIPPINCOTT WILLIAMS & WILKINS, PHILADELPHIA, US, vol. 66, no. 12, 27 June 2006 (2006-06-27) , pages 1920-1922, XP008145543, ISSN: 0028-3878, DOI: 10.1212/01.WNL.0000219761.05466.43 See abstract; page 1920, column 2, paragraph 4 --- WO 2019/073379 A1 (COMPASS PATHWAYS LTD [GB]) 18 April 2019 (2019-04-18) paragraphs [0099], [0102] - [0104], [0112]; claims 1,8,13-18,21,24; table 40 ---	1-3, 7-11,32, 33,59, 111, 126-129 1-111, 126-162 1-111, 126-162 1-3,7,8, 32-34, 36-38, 40-46, 48-53, 56-63, 111, 128-130, 132-141, 145-149, 160-162
A		
A		
X,P		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/053688

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-106, 117, 126, 127(completely); 107-111, 128-162(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-106, 117, 126, 127(completely); 107-111, 128-162(partially)

Method of treating depression,Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Bipolar I Disorder, Bipolar II Disorder, or Cyclothymic Disorder;Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition comprising administering an effective amount of psilocybin or an active metabolite thereof

---

2. claims: 107-111, 128-162(all partially)

Method of treating Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Post-Traumatic Stress Disorder (PTSD), Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder,Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder comprising administering an effective amount of psilocybin or an active metabolite thereof

---

3. claims: 107-111, 128-162(all partially)

Method of treating treating Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder) comprising administering an effective amount of psilocybin or an active metabolite thereof

---

4. claims: 107-111, 128-162(all partially)

Method of treating Migraines, Cluster Headaches such as

Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache comprising administering an effective amount of psilocybin or an active metabolite thereof

---

5. claims: 107-111, 128-162(all partially)

Method of treating Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder comprising administering an effective amount of psilocybin or an active metabolite thereof

---

6. claims: 107-111, 128-162(all partially)

Method of treating Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, or Kleptomania comprising administering an effective amount of psilocybin or an active metabolite thereof

---

7. claims: 113, 114, 118(completely); 107-112, 123, 128-162(partially)

Method of treating Neurocognitive Disorders due to Alzheimer's, Lewy Bodies, Traumatic Brain Injury, Prion Disease, HIV Infection, Parkinson's, or Huntington's; Language Disorder, Dysphasia (laguage disorder from brain disease or damage); Speech Sound Disorder (Phonological Disorder); Childhood-Onset Fluency Disorder (Stuttering); Social (Pragmatic) Communication Disorder; Tourette's Disorder; Persistent (Chronic) Motor or Vocal Tic Disorder; Amnestic Disorder Due to Known Physiological Condition; Retrograde Amnesia; Insomnia Disorder, Hypersomnolence Disorder, Narcolepsy, or Primary Central Sleep Apnea.; Intellectual Disabilities; Suicidal Behavior Disorder, Nonsuicidal Self-Injury, Persistent Complex Bereavement Disorder; Epilepsy or Amyotrophic Lateral Sclerosis (ALS); Autism Spectrum Disorder or Antisocial Personality Disorder; Attention-Deficit/Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder; or Unspecified Attention-Deficit/Hyperactivity Disorder comprising administering an effective amount of psilocybin or an active metabolite thereof

---

8. claims: 107-110, 112, 123, 128-162(all partially)

Method of treating concussion; chronic traumatic encephalopathy (CTE); Transient Cerebral Ischemic Attack, Cerebral Infarction, Cerebral Bleeding; Progressive Supranuclear Ophthalmoplegia; stroke ; Traumatic Brain Injury, Neurodegeneration, locked-in syndrome comprising administering an effective amount of psilocybin or an active metabolite thereof

---

9. claims: 115, 119(completely); 107-110, 123, 128-162(partially)

Method of treating Schizotypal (Personality) Disorder, Delusional Disorder, Schizophrenia, or Schizoaffective Disorder; Schizoid Personality Disorder, Schizotypal Personality Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, Obsessive-Compulsive Personality Disorder; Mania comprising administering an effective amount of psilocybin or an active metabolite thereof

---

10. claims: 116(completely); 107-110, 123, 128-162(partially)

Method of treating Female Sexual Interest/Arousal Disorder, Male Hypoactive Sexual Desire Disorder, or Excessive Sexual Drive; Paraphilic disorders comprising administering an effective amount of psilocybin or an active metabolite thereof

---

11. claims: 120(completely); 107-110, 128-162(partially)

Method of treating age-related hearing loss or tinnitus comprising administering an effective amount of psilocybin or an active metabolite thereof

---

12. claims: 121(completely); 107-110, 123, 128-162(partially)

Method of treating Multiple Sclerosis, Cranial Nerve Disorder, Neuromyelitis Optica, Bell's Palsy, Guillain Barre Syndrome, Demyelinating Disease of Central Nervous System, or Chronic Inflammatory Demyelinating Polyneuritis; Myelopathy, comprising administering an effective amount of psilocybin or an active metabolite thereof

---

13. claims: 107-110, 123, 128-162(all partially)

Method of treating GI Tract Related Diseases, Sickle Cell Disease, restless leg syndrome comprising administering an effective amount of psilocybin or an active metabolite thereof

---

14. claims: 122(completely); 107-110, 128-162(partially)

Method of treating pain administering an effective amount of psilocybin or an active metabolite thereof

---

15. claims: 124, 125(completely); 107-110, 128-162(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method of treating a subject to improve cognition comprising administering an effective amount of psilocybin or an active metabolite thereof

---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2020/053688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018135943 A1	26-07-2018	CA 3050679 A1	26-07-2018
		EP 3570830 A1	27-11-2019
		US 2019350949 A1	21-11-2019
		WO 2018135943 A1	26-07-2018
WO 2018148605 A1	16-08-2018	AU 2018217829 A1	12-09-2019
		BR 112019016489 A2	07-04-2020
		CA 3052974 A1	16-08-2018
		CN 110740728 A	31-01-2020
		EP 3579832 A1	18-12-2019
		JP 2020506246 A	27-02-2020
		US 2018221396 A1	09-08-2018
		WO 2018148605 A1	16-08-2018
WO 2019073379 A1	18-04-2019	AU 2018349279 A1	28-05-2020
		CA 3078765 A1	18-04-2019
		CN 111491919 A	04-08-2020
		CO 2020005643 A2	15-05-2020
		DE 202018006384 U1	19-03-2020
		EP 3694835 A1	19-08-2020
		GB 2571696 A	11-09-2019
		GB 2572023 A	18-09-2019
		GB 2576059 A	05-02-2020
		KR 20200085753 A	15-07-2020
		US 2019119310 A1	25-04-2019
		US 2020199161 A1	25-06-2020
		WO 2019073379 A1	18-04-2019