

Study Protocol

Official Title

A Randomized, Double-Blind Study of Single-Dose
Psilocybin for Major Depressive Disorder (MDD)

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2881 Woods Hollow Rd, Madison, WI 53711



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A Randomized, Double-Blind Study of Single-Dose
Psilocybin for Major Depressive Disorder (MDD)

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PROTOCOL AMENDMENTS

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SPONSOR SIGNATORY

This study protocol was subject to critical review and has been approved by the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the Investigational Product (IP)
- The moral, ethical and scientific principles of Good Clinical Practice (GCP) as described in Title 21 of the United States Code of Federal Regulations (21 CFR) parts 50, 54, 56 and 312 and according to applicable local requirements.

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

Charles L. Raison

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approved this document.
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12-Mar-2021

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LIST OF ABBREVIATIONS

21 CFR	Title 21 of the Code of Federal Regulations
AD	Antidepressant
AE	Adverse Event
ATRQ	Massachusetts General Hospital Antidepressant Treatment History Questionnaire
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
BP	Blood Pressure
CBC	Complete Blood Count
CGI-S	Clinical Global Impression—Severity
CIOMS	Council for International Organizations of Medical Sciences
CMP	Complete Metabolic Panel
CoC	Certificate of Confidentiality
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
<i>d</i>	Cohen's <i>d</i>
DBS	Deep Brain Stimulation
DEA	Drug Enforcement Agency
DESS	Discontinuation Emergent Signs and Symptoms
DHQ	Drug History Questionnaire
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition
DSMB	Data and Safety Monitoring Board
DUDIT	Drug Use Disorders Identification Test
EBI	Emotional Breakthrough Inventory
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessments
ECT	Electroconvulsive Therapy
ED	Emergency Department
EDC	Electronic Data Capture
Emmes	The Emmes Company
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act of 2002
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Scale
<i>g</i>	Hedges <i>g</i>

HDPE	High-Density Polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
Hopkins	Johns Hopkins University
HPMC	Hydroxypropyl Methylcellulose
HPPD	Hallucinogen-Persisting Perception Disorder
HR	Heart Rate
Hrs	Hours
HRT	Hormonal Replacement Therapy
hs-CRP	High-Sensitivity C-Reactive Protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
LICQ	Lifetime Illness Characteristic Questionnaire
LSD	Lysergic Acid Diethylamide
MADRS	Montgomery-Asberg Depression Rating Scale
MAOIs	Monoamine Oxidase Inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MEQ-30	Mystical Experience Questionnaire
MD	Medical Doctor
MDD	Major Depressive Disorder
MDMA	3,4-Methylenedioxy-methamphetamine
mm Hg	Millimeters of Mercury
MMRM	Mixed-effect Model with Repeated Measures
MoP	Manual of Procedures
NIST	National Institute of Standards and Technology
NP	Nurse Practitioner
NYU	New York University
ODQ	Oxford Depression Questionnaire
OMB	Office of Management and Budget
<i>p</i>	Probability
PCP	Phencyclidine
PI	Principal Investigator
QIDS	Quick Inventory of Depressive Symptomatology

Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
Rebar	Rebar Interactive
rTMS	Repetitive Transcranial Magnetic Stimulation
RX	Prescription/ treatment/ dose
SAEs	Serious Adverse Events
SAMe	S-adenosyl-methionine
SAP	Statistical Analysis Plan
SaS	Set and Setting Protocol
SCC	Study Coordinating Center
SCID	Structured Clinical Interview for DSM-5
SCID-II	Structured Clinical Interview for DSM-IV Axis II Personality Disorders
SCID-5-PD	Structured Clinical Interview for DSM-5 – Personality Disorder
SCID-5-SPQ	SCID - Screening Personality Questionnaire
SCID-CT	Structured Clinical Interview for DSM-5 – Clinical Trials Version
SCID-RV	SCID – Research Version
SDS	Sheehan Disability Scale
SMDDS	Symptoms of Major Depressive Disorder Scale
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
TBI	Traumatic Brain Injury
TCAs	Tricyclic Agents
TEAE	Treatment Emergent Adverse Event
TLFB	Timeline Followback
THC	Tetrahydrocannabinol
TIA	Transient Ischemic Attack
TMS	Transcranial Magnetic Stimulation
TRD	Treatment-Resistant Depression
TSH	Thyroid Stimulating Hormone
VNS	Vagus Nerve Stimulation
WOCBP	Woman of Childbearing Potential

PROTOCOL SYNOPSIS

Title

A Randomized, Double-Blind Study of Single-Dose Psilocybin for Major Depressive Disorder (MDD)

Study Code

PSIL201

Name of Sponsor

Usona Institute
2800 Woods Hollow Rd
Madison, WI 53711

Medical Monitor



The Emmes Company
401 N. Washington St., #700
Rockville, MD 20850

Phase of Study

Phase 2

Sample Size

~100 randomized

Name of Investigational Product (IP)

Psilocybin 3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate

Name of Active Placebo

Niacin

ClinicalTrials.gov Identifier

NCT03866174

Description of IP and Active Placebo

Study Intervention Name:	Psilocybin (active drug product)	Niacin (active placebo product)
Dosage formulation:	One active capsule contains 25 mg of psilocybin	One active placebo capsule contains 100 mg of niacin
Capsule:	Size 2 hydroxypropyl methylcellulose (HPMC), opaque	Size 2 HPMC, opaque
Unit dose strength:	25 mg	100 mg
Route of Administration:	Oral (solid dose)	Oral (solid dose)
Dosing instructions:	One capsule administered with water	One capsule administered with water
Packaging and Labeling:	Study Intervention will be provided in a high-density polyethylene (HDPE) bottle. Each bottle will contain one capsule (psilocybin or niacin) and will be labeled as required per country requirement for blinded study.	

Study Description and Overview

One hundred participants (males and females) ages 21 to 65 who, at Screening, meet DSM-5 criteria for major depressive disorder (MDD), have a current depressive episode of at least 60-day duration, have a Screening Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 28 and meet all other inclusion/exclusion criteria will be stratified by study site and randomized with a 1-to-1 allocation under double-blind conditions to receive a single 25 mg oral dose of psilocybin or a single 100 mg oral dose of niacin. Niacin will serve as an active placebo control that provides an acute physiological response (flushing) that is intended to aid in blinding of intervention allocation. All randomized participants will be included in the intent-to-treat (ITT) population for testing primary, secondary and exploratory study endpoints.

Only participants who meet depressive symptom severity criteria at Screening (Screening MADRS score ≥ 28 on both the central rater and computer assessments) and who do not show an unacceptably large degree of symptom improvement between the Screening visit and the Baseline assessment (indexed by $\leq 30\%$ improvement on both the central rater and computer MADRS assessments) will be eligible for randomization. In addition, at Screening and Baseline, only participants with a score difference ≤ 7 between the central rater and computer MADRS assessments will be eligible for randomization. A larger discrepancy has been associated with an exceptionally high placebo response in prior studies conducted by the study's central rater vendor (*data on file*). In addition, inability to be consistent in response to the same questions likely identifies individuals not sufficiently capable of providing reliable responses.

Potential participants who meet all other entry criteria at Screening but who are taking an antidepressant or an antidepressant plus an augmenting agent (e.g., a second antidepressant, an atypical antipsychotic, lithium) will be eligible for continuation in the study but will enter a medication taper during which current psychotropic medications will be withdrawn under the supervision of a study psychiatric medical provider. Participants will be eligible to undergo the Baseline assessment at least 2 weeks after the last dose of the applicable medication taper.

Participants deemed eligible following successful completion of all screening assessments will complete central rater, site rater and self-report measures at Baseline for a final eligibility determination. Eligible participants at Baseline will undergo preparation sessions and be eligible for randomization on Dosing Day to receive either psilocybin or niacin active-placebo and will complete follow-up visits and assessments on study Day 2, 8, 15, 29 and 43 (within corresponding visit windows). Study outcome measures will assess depressive symptoms, clinical global functioning, functional disability, anxiety symptoms and health-related quality of life. Safety outcome measures will be collected at all assessment time points from the time of consent through the end of study.

To enhance participant safety, the current study does not propose to test psilocybin as a “context-less” pharmacological agent, but rather within a “set and setting” (SaS) protocol similar to the protocol that has been used in all modern studies of psilocybin in both diseased and normal healthy populations. The SaS protocol for this study includes: 1) a period of preparation with session Facilitators prior to dosing; 2) administration of study medications in an aesthetically pleasing room under the supervision of two Facilitators who are present throughout the session (with the exception of short, temporary allowances for facilitator breaks; e.g. bathroom breaks); and 3) three post-dose integration sessions during which participants are encouraged to discuss their intervention experience with the Facilitators. The SaS will be identical for those randomized to psilocybin or niacin active placebo.

Study Duration

The planned maximum study duration for each participant will be approximately 12 weeks (87 days), with variation primarily dependent on the length of the screening period, the number of days between baseline and dosing, and the visit windows provided for each post-dose assessment.

Primary Objective

The primary objective of this study is to evaluate the potential efficacy of a single 25 mg oral dose of psilocybin for major depressive disorder (MDD) compared to an active placebo (niacin) in otherwise medically healthy participants between the ages of 21 and 65, assessed as the difference between groups in changes in depressive symptoms from Baseline to Day 43 post-dose.

Primary Outcome Measure

Central rater administered MADRS

Secondary, Exploratory and Exploratory-Mechanism Based Objectives

The key secondary objective is to evaluate the potential efficacy of a single 25 mg dose of psilocybin for MDD compared to an active placebo in medically healthy participants ages 21 to 65, measured as between-group difference in change in MADRS-assessed depressive symptoms from Baseline to Day 8. Additional secondary, exploratory, and exploratory-mechanism based objectives are to evaluate depressive symptoms at other time points and to assess between-group differences in rates of sustained response and remission, clinical global functioning, anxiety symptoms, functional disability, health-related quality of life, mystical-type experiences, and emotional breakthrough experiences.

Secondary, Exploratory, and Exploratory-Mechanism Based Outcome Measures

Secondary: MADRS (Day 8 key secondary), Sheehan Disability Scale (SDS); **Exploratory:** Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression – Severity (CGI-S), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q); Symptoms of Major Depressive Disorder Scale (SMDDS), Oxford Depression Questionnaire (ODQ); **Exploratory-Mechanism Based:** 30-item Mystical Experience Questionnaire (MEQ-30), and Emotional Breakthrough Inventory (EBI)

Safety Objectives

The overall safety objective of this study is to evaluate a single 25 mg oral dose of psilocybin compared to an active placebo in incidence, severity and frequency of Adverse Events (AEs), Treatment Emergent AEs (TEAEs), Solicited AEs, and Serious Adverse Events (SAEs) before, during and after the dosing session and at all follow-up visits.

- 1) Period 1 (Screening Period): Screening through end of Baseline;
- 2) Period 2 (Preparation Period): Preparation until Randomization;
- 3) Period 3 (Dosing Period): Randomization through Day 9; and
- 4) Period 4 (Follow-up Period): Day 10 through Day 43

Solicited Adverse Events

The following solicited AEs will be collected:

Visual perceptual effects (Periods 3-4) will be solicited by asking the following questions: 1) *Since your dosing session have you experienced any uncontrolled or disturbing return of study drug effects?*, and 2) *Since your dosing session have you experienced any visual distortions (e.g. geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified color, trails for images of moving objects, positive after-images, halos around objects)?* If a participant reports “Yes” to any of the above questions a study psychologist or psychiatrist will follow up for further assessment/diagnosis.

Additional solicited AEs include:

- Active suicidal ideation identified through the C-SSRS and/or MADRS and verified by clinical assessment (recorded for Periods 1-4; would result in [screen failure](#) or [early termination](#) in Periods 1-2)
- Headache (Period 3); and
- Nausea (Period 3); and
- Elevated blood pressure (BP) as defined by systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg on three separate readings and requiring medication (recorded for Periods 1-4; may result in [screen failure](#) or [early termination](#) in Periods 1-2); and
- Elevated heart rate (HR) as defined as >100 beats per minute (BPM) and requiring medication (recorded for Periods 1-4; may result in [screen failure](#) or [early termination](#) in Periods 1-2); and
- Drug overdose with suicidal intent (recorded for Periods 1-4; would result in [screen failure](#) or [early termination](#) in Periods 1-2)

Unsolicited Adverse Events

Any other observed and participant reported AEs and SAEs will be recorded for all study periods (Periods 1-4), following written informed consent. SAEs will be reported per FDA guidelines.

Specific Safety Monitoring Objectives

Safety will be continually evaluated by study staff through monitoring and assessment of AEs, vital signs, concomitant medication use, physical exams, safety labs, site rater administered measures, and integration with session Facilitators. The study will also assess abuse liability, including non-clinical, illicit use of psilocybin and other psychedelics and other illicit and non-prescribed drug use via the AUDIT and DUDIT, Timeline Followback, and Substance Use Disorders module of the SCID-CT, participant self-report, and urine drug testing per the Schedule of Assessments ([Table 1](#)). Additionally, a Data and Safety Monitoring Board (DSMB) will review and oversee safety data.

Eligibility and Safety Measures

Structured Interview for DSM-5 Disorders-Clinical Trials Version (SCID-5-CT), SCID-5-Personality Disorders (PD), Alcohol Use Disorders Identification Test (AUDIT), Drug Use Disorders Identification Test (DUDIT), Timeline Followback (TLFB), Drug History Questionnaire (DHQ), Columbia Suicide Severity Rating Scale (C-SSRS), Lifetime Illness Characteristic Questionnaire (LICQ), Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ), and the Family History Screen (FHS).

Inclusion/ Exclusion Criteria

Inclusion Criteria

Individuals eligible to be randomized in this protocol are those who meet *all* of the following criteria:

1. Are 21 to 65 years old at the time of written informed consent at the Screening visit
2. Are able to read, speak, and understand English
3. Are able and willing to adhere to study requirements, including attending all study visits, preparatory and follow-up sessions, and completing all study evaluations
4. Are able to swallow capsules
5. Women of childbearing potential (WOCBP) must agree to practice an effective means of birth control throughout the duration of the study, from Screening through the Day 43 assessment (see [Section 15](#) Pregnancy for a definition of WOCBP)
6. Meet DSM-5 criteria for a diagnosis of major depressive disorder and are currently experiencing a major depressive episode of at least a 60-day duration at the time of the Screening
7. Have sustained moderate-severe depression symptoms at Screening and Baseline, as defined by a Screening MADRS total score ≥ 28 and $\leq 30\%$ improvement (i.e. decrease) in MADRS total score from Screening to Baseline on both the central rater and computer assessments
8. Central rater MADRS and computer administered MADRS total scores show ≤ 7 point difference between scores at both Screening and Baseline
9. Have an identified support person
 - a. Agree to be accompanied home (or to an otherwise safe destination) by the support person, or another responsible party, following dosing

Exclusion Criteria

Individuals not eligible to be randomized in this protocol are those who meet *any* of the following criteria:

1. Women who are pregnant, as indicated by a positive urine pregnancy test at Screening or Baseline. Women who intend to become pregnant during the study or who are currently nursing.
2. Unwilling or unable to discontinue formal psychotherapy ([Section 4.2.2](#))
3. Unwilling to discontinue any current prescription or supplemental psychotropic agents (including trazodone for sleep) or are unable according to [Section 4.2.1 Medication Taper](#)
 - o Note: Benzodiazepine medications and non-benzodiazepine sleeping medications will be allowed to continue through the study period for participants who have been on a stable dose of such a medicine for at least 6 weeks prior to Screening.
4. Have previously received the following non-medication treatments:
 - a. deep brain stimulation (DBS)
 - b. vagus nerve stimulation (VNS)

5. Currently receiving electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)
 - Note: Previous treatment with ECT or TMS is allowed as long as last treatment was ≥ 90 days from the time of Screening
6. Unable or unwilling to discontinue any current medications having a primary centrally-acting serotonergic effect, including monoamine oxidase inhibitors (MAOIs) or dopaminergic antagonists
 - Note: Any prohibited agents must have been stopped at least 5x the elimination half-life of the specific drug at the time of Baseline. See [Appendix A](#) for a full list of prohibited medications.
7. Unable or unwilling to discontinue any current medications that are known uridine diphosphate (UDP) or glucuronosyltransferase (UGT) enzyme modulators, such as valproate
 - Note: Any prohibited agents must have been stopped at least 5x the elimination half-life of the specific drug at the time of Baseline. See [Appendix A](#) for a full list of prohibited medications.
8. Report the following psychedelic substances use:
 - a. Have used a psychedelic substance in the previous 5 years; or
 - b. Have used psychedelic substances > 10 times in their lifetime
 - Note: Psychedelic substances include psilocybin, Lysergic acid diethylamide (LSD), mescaline (and natural products containing mescaline including peyote and San Pedro cactus), N,N-Dimethyltryptamine (DMT), natural products containing DMT including ayahuasca and 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT), ibogaine, 2C compounds, 3,4-methylenedioxy-methamphetamine (MDMA), methylone or other psychedelics.
9. Have the following cardiovascular conditions:
 - a. coronary artery disease, congenital long QT syndrome (prior diagnosis), cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction (prior diagnosis);
 - b. tachycardia (defined as heart rate > 100 beats per minute);
 - c. a clinically significant Screening ECG abnormality (e.g., atrial fibrillation);
 - Note: A QTcF interval > 450 milliseconds is considered a clinically significant ECG abnormality
 - d. artificial heart valve; or
 - e. any other significant current or history of cardiovascular condition, based on the clinical judgment of study physician, that would make a participant unsuitable for the study
10. At Screening or Baseline have elevated blood pressure as defined as:
 - a. Screening blood pressure SBP > 135 mmHg or DBP > 85 mmHg on three separate readings; or
 - b. Baseline blood pressure SBP > 140 mmHg or DBP > 90 mmHg on three separate readings
 - Note: Please see justification for blood pressure parameters in [Section 4.2.8](#)
11. Have a history of stroke or Transient Ischemic Attack (TIA)
12. Have moderate to severe hepatic impairment, as indexed by a Child-Pugh score ≥ 7
13. Have epilepsy

14. Have insulin-dependent diabetes
 - Note: Participants who are taking oral hypoglycemic agent and have a history of hypoglycemia requiring medical intervention will be excluded
15. Are unable or unwilling to adhere to the following medication requirements:
 - a. Agree to suspend sildenafil (Viagra®), tadalafil, or similar medications at least 72 hours prior to dosing
 - b. If taking any supplement containing >20 mg of niacin, agrees to suspend use for at least five days prior to dosing and for the duration of the study
16. Have a positive urine drug test including Amphetamines, Barbiturates, Buprenorphine, Benzodiazepines, Cocaine, Cannabis, Methamphetamine, MDMA, Methadone, Opiates (Morphine, Oxycodone), Phencyclidine (PCP), and Tetrahydrocannabinol (THC).

Exceptions are made for prescribed Benzodiazepines (stable dose for sleep or anxiety).

 - Note: Prescribed benzodiazepine medications and non-benzodiazepine sleeping medications will be allowed to continue through the study period for participants who have been on a stable dose of such a medicine for at least 6 weeks prior to Screening, as determined during review of concomitant medications.
 - Note: Participants using cannabis, including legal cannabis, for any purposes must agree to refrain from use beginning at Screening, as confirmed with a negative Baseline drug test, and through to the end of the study.
 - Note: Participants who are taking prescription maintenance methadone or buprenorphine naloxone will be excluded.
 - Note: Prescription opiates must have been stopped at least 5x the elimination half-life of the specific drug at the time of dosing, as confirmed with a negative urine drug screen on Day 1 (prior to dosing). They can resume use following the Integration Session # 1 the day after dosing.
 - Note: Participants using prescribed psychostimulants (amphetamines and Ritalin), must agree to refrain from use two weeks prior to baseline visit, as confirmed with a negative Baseline drug test, and through to the end of the study.
 - Note: Participants using prescribed trazodone for sleep (at any dose) must agree to refrain from use two weeks prior to baseline visit and through to the end of the study.
17. Nicotine dependence that would disallow an individual to be nicotine free for the 7-10 hours during the dosing period
18. Meet DSM-5 criteria for schizophrenia spectrum or other psychotic disorders, including MDD with psychotic features (except substance/medication-induced or due to another medical condition), or Bipolar I or Bipolar II Disorder
 - Note: Participants with any lifetime diagnosis of schizophrenia spectrum or other psychotic disorders will be excluded
19. Meet DSM-5 criteria for antisocial personality disorder
20. Meet DSM-5 criteria for a moderate or severe alcohol or drug use disorder (excluding caffeine)
 - Note: Participants with a diagnosis of alcohol or drug use disorder within the past 12 months will be excluded
21. Have presence of any psychiatric condition or symptom judged by the PI (or designee) to be a more significant clinical problem than MDD for the participant, including a DSM-5 personality disorder

22. Have a first-degree relative with schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or Bipolar I Disorder
23. Have a psychiatric condition judged to be incompatible with establishment of rapport with the Facilitators or safe exposure to psilocybin
24. Report the following suicidal ideation or suicidal thoughts defined as:
 - a. Answer 'Yes' to C-SSRS Suicidal Ideation items 4 or 5 within the last 2 months at Screening or "since last visit" at Baseline;
 - b. Report having had any C-SSRS Suicidal Behavior item within the past 12 months at Screening or "since last visit" at Baseline, as defined by 'Yes' to any of the following on the C-SSRS: actual attempt, interrupted attempt, aborted attempt, or preparatory acts; or
 - c. Have a score of ≥ 5 on Item 10 (suicidal thoughts) of the central-rater or computer administered MADRS at Screening or Baseline; or
 - d. Have any suicidal ideation or thoughts, in the opinion of the study physician or PI, that presents a serious risk of suicidal or self-injurious behavior at any time prior to randomization
25. Have any suicidal ideation or thoughts, in the opinion of the study physician or PI, that presents a serious risk of suicidal or self-injurious behavior
26. Have any physical or psychological symptom, medication or other relevant finding prior to randomization, based on the clinical judgment of clinical/medical study personnel, that would make a participant unsuitable for the study.
27. Have an allergy or intolerance to any of the materials contained in either drug product

Statistical Analysis

This Phase 2 study has been powered to evaluate the clinical efficacy of psilocybin for the primary and key secondary objectives, i.e. to test the difference between psilocybin and niacin in the change in central rater MADRS score from Baseline to Day 43 and Day 8, respectively, in the randomized analysis set. Two open-label studies of psilocybin in MDD (Davis et al., 2019) and TRD (Carhart-Harris et al., 2016) indicated 62% to 69% mean reduction in depression symptoms 1-week following the final dosing session in the psilocybin arms, and this reduction was sustained at 4-5 weeks post dosing with reduction in depression symptoms of 57% to 66% ([Table 8](#)). Two prior studies of psilocybin in cancer-related depression and anxiety showed a similar trend with a mean reduction in depressive symptoms at 5 weeks post dose of 71% in the high-dose group in Griffiths et al., 2016, and 57% reduction at 6 weeks post dose in Ross et al., 2016. Based on prior controlled studies of psilocybin in cancer-related depression and anxiety (Ross et al., 2016), a decrease in depression symptoms from baseline to 43 days post-dose of approximately 30% in the niacin active-control arm is expected.

Approximately 100 patients are planned to be randomized into this study. Assuming a placebo group MADRS mean change from baseline = 10 at all time points, MADRS change from baseline SD = 10, psilocybin group MADRS mean change from baseline at Day 8 = 18 ($d = 0.8$) and Day 43 = 17 ($d = 0.7$), and 12.5% overall dropout by Day 43, a sample size of 100 participants would result in 92% power for primary Day 43 endpoint and 98% power for the key

secondary Day 8 endpoint. Key assumptions are in alignment with what has been observed in previous psilocybin studies.

In the final intent to treat (ITT) analysis, a mixed effect model for repeated measures (MMRM) with an unstructured or other appropriate covariance matrix, with Baseline questionnaire score as a covariate and site, sex, and TRD status as fixed effects will be employed to test primary and key secondary study endpoints.

1 INTRODUCTION

1.1 Usona Institute

Usona Institute (Usona) is a non-profit medical research organization founded in 2014. As part of its mission to explore the therapeutic effects of consciousness-expanding medicines, Usona is conducting research to further understand the therapeutic effects of psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate). The purpose of this study is to evaluate the safety and efficacy of psilocybin for major depressive disorder (MDD) in the general population (under Investigational New Drug [IND] #129532).

1.2 Purpose

The overarching purpose of this study is to conduct an initial examination of the safety, efficacy and tolerability of single-dose psilocybin in otherwise medically healthy patients with MDD. The overall objectives of this study are to examine the potential efficacy of a single, fixed, 25 mg oral dose of psilocybin in reducing depressive and anxious symptoms and improving functional disability and quality of life in medically healthy patients with MDD when compared to active placebo; and to collect safety and tolerability data on single-dose psilocybin intervention in medically healthy patients with MDD. Of note, this study represents the first randomized, double-blind, placebo-controlled study of single-dose psilocybin in a general-population (i.e. medically healthy) MDD sample (prior studies of depression have either used an open design or occurred in patients with a concomitant medical illness).

1.3 Study Rationale

MDD is currently the leading cause of disability in the world (<http://www.who.int/mediacentre/factsheets/fs369/en/>). This highlights the urgent need to identify and test novel pharmacological agents that might benefit depressed patients who have not achieved symptom remission with currently approved antidepressant modalities. Recent studies suggest that psilocybin produces a substantial and sustained improvement in depressive symptoms following a single administration.

1.4 Background

1.4.1 Major Depressive Disorder (MDD)

Major depression has become a health crisis of epidemic proportions in the modern world (<http://www.who.int/mediacentre/factsheets/fs369/en/>). The prevalence of major depression has risen over the last several generations in every country examined (Weissman et al., 1992) and age of symptom onset has decreased (Chengappa et al., 2003). It is estimated that major depression will rank second after cardiac disease as a cause of international medical morbidity by the year 2020 (Global Burden of Disease Study, 2015). One in six individuals in the United States will experience an episode of major depression in his or her lifetime (Kessler et al., 2003), and the risk of subsequent episodes rises dramatically once a person has been depressed (Frank, Kupfer, Wagner, McEachran, & Cornes, 1991). Indeed, depression is now recognized to be a highly chronic and recurrent illness (Frank et al., 1990; Greden, 2001b). On average, patients with major depression are symptomatic 60% of the time, even when receiving community-

standard antidepressant treatment (Judd et al., 1998). Recent estimates place the economic burden of depression in the United States at 200 billion dollars a year (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). Depression is associated with greater disability than are most other chronic illnesses and is a risk factor for mortality (Wulsin, Vaillant, & Wells, 1999). Suicide ranks among the top ten causes of death in the United States (Akiskal, 2005), and best estimates suggest that 60-70% of people who kill themselves are clinically depressed (Sudak, 2005). Between 10-15% of severely depressed people eventually commit suicide (Sudak, 2005). In addition, many studies indicate that depression significantly increases all-cause mortality independently of suicide (Wulsin et al., 1999). Depression predicts the later development of a number of medical conditions, including cardiac and cerebrovascular disease (Joynt, Whellan, & O'Connor, 2003; Thomas, Kalaria, & O'Brien, 2004), hypertension (Davidson, Jonas, Dixon, & Markovitz, 2000; Jonas & Lando, 2000), diabetes (Eaton, Armenian, Gallo, Pratt, & Ford, 1996; Kawakami, Takatsuka, Shimizu, & Ishibashi, 1999), obesity and metabolic syndrome (Barefoot et al., 1998; Pine, Goldstein, Wolk, & Weissman, 2001; Raikonen, Matthews, & Kuller, 2002), dementia (Jorm, 2001), and cancer (Spiegel & Giese-Davis, 2003). Depression also markedly increases mortality in medically ill patients and has been associated with decreased responses to pharmacological treatments for cancer and hepatitis C (Raison et al., 2005; Spiegel & Giese-Davis, 2003).

Unfortunately, most patients with depression do not experience a complete resolution of symptoms with antidepressant treatment (Greden, 2001a). The risks of not responding completely to (or tolerating) treatment have been highlighted by recent studies documenting that partial—but incomplete—response is associated with an increased risk of full symptomatic relapse (even when on therapy) and a worse long term disease course, as well as with significantly impaired quality of life (Judd et al., 2000; Miller et al., 1998; Simon, 2000). Combined with the high prevalence and significant disability associated with MDD, the fact that currently available treatments are not fully adequate highlights the tremendous need to identify novel treatment strategies.

1.4.2 Psilocybin

Psilocybin is a natural product produced by numerous species of *Psilocybe* mushrooms. The phosphate group is enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which for its behavioral effects is the 5-HT_{2A} receptor (Carhart-Harris et al., 2014; Nichols, 2004). Psilocybin was first isolated from *Psilocybe* mushrooms in 1957, followed by *de novo* synthesis in 1958 (Passie, Seifert, Schneider, & Emrich, 2002). Psilocybin was marketed worldwide by Sandoz in the 1960s as *Indocybin*[™] for experimental and psychotherapeutic purposes. Although it was well tolerated and demonstrated potentially useful effects, it was classified as a controlled substance, placed in Schedule I in 1970, and effectively removed from clinical use or scientific study. Psilocybin, and similar drugs such as lysergic acid diethylamide (LSD) and mescaline, fall into a pharmacological class referred to in this application as “classic psychedelics” to differentiate them from other psychoactive substances (i.e. MDMA [3,4-methylenedioxy-methamphetamine] that have different psychological/ behavioral effects and different adverse effect profiles and risk/benefit ratios than psilocybin (Carhart-Harris & Nutt, 2013; Nutt, King, Phillips, & Independent Scientific Committee on, 2010).

Psilocybin is currently a Schedule I controlled substance, which means it is considered to have high potential for abuse and no currently accepted medical use, according to the Drug Enforcement Agency (DEA). The psilocybin used in this study is synthetically manufactured in a laboratory and meets quality specifications suitable for human research use. No mushrooms naturally containing psilocybin are used in the manufacturing process. The active drug is encapsulated using a hydroxypropyl methylcellulose (HPMC) capsule and contains 25 mg of psilocybin. The active placebo is encapsulated using a HPMC capsule and contains 100 mg of niacin USP. Psilocybin and niacin are administered orally and taken with water.

Information regarding the pharmacology and toxicology of psilocybin can be found in the [Investigator's Brochure](#) (IB).

1.4.3 Previous Clinical Experience with Psilocybin Relevant to MDD

Data reaching back to the 1960s suggest that classic psychedelics, including psilocybin, have behavioral effects relevant to the treatment of depression. Recent studies (Carhart-Harris et al., 2016; R. R. Griffiths et al., 2016; Ross et al., 2016) suggest that psilocybin may possess antidepressant properties. Specifically, two randomized, double-blind, placebo-controlled studies in patients with life-threatening cancer and clinically-significant depression/anxiety and an open trial in patients with Treatment-Resistant Depression (TRD) suggest that a single intervention with psilocybin conducted within a set and setting (SaS) protocol, described below, produces antidepressant effects that are sustained for up to six months post- intervention, while having a minimal, time-limited side effect profile (Carhart-Harris et al., 2016; R. R. Griffiths et al., 2016; Ross et al., 2016). More recently a small randomized, wait-list controlled trial of two doses of psilocybin in the range proposed for the current protocol produced a large improvement in depressive symptoms, whether assessed as change from baseline or in comparison to the wait-list condition (Davis et al., 2020).

The current proposal advances our knowledge of the value of single-dose psilocybin for the treatment of MDD in several ways. To date, placebo-controlled studies of psilocybin to treat depression have only been conducted in patients with cancer, not in medically healthy patients. And the single 12 participant study conducted to date of psilocybin intervention in medically healthy patients with TRD was not blinded and did not include a placebo condition. The recent wait-list controlled trial in MDD also did not have a placebo condition and no allocation blinding was done. The scientific rationale for the current study is that it will address both these gaps in understanding the potential value of single dose psilocybin for MDD in medically healthy patients. Specifically, this study will address this research gap by: 1) randomizing a population of medically healthy participants with MDD; 2) utilizing a randomized, double-blind, placebo-controlled, parallel-group design to control for baseline covariates, placebo and other therapeutic effects not specifically linked to medication exposure; and 3) utilizing an offsite independent centralized rating service to reduce the risk of functional unblinding of raters assessing the study's primary endpoint.

In addition, data derived from this study will allow for a refinement of effect size estimates for larger studies of single dose psilocybin in MDD. Moreover, because previous psilocybin studies

utilized weight-based dosing, the current study will allow us to examine whether fixed-dose psilocybin will produce effect size benefits consistent with those seen with weight-based dosing.

1.5 The Set and Setting (SaS) Protocol

Early studies with psilocybin, administered for research purposes but without a supportive setting, observed a wide range of responses, including panic reactions and episodes of paranoia that were highly distressing (R. R. Griffiths et al., 2011; R. R. Griffiths, Richards, McCann, & Jesse, 2006). From these early experiments came an increasing appreciation of the importance of designing the optimal conditions under which psilocybin could be safely administered within the research setting. Such attention was aimed at reducing the risk of these negative responses while simultaneously increasing the likelihood of participants having the types of positive mystical-type experiences that appear to play an important causal role in long-term positive behavioral/emotional changes. By addressing what are now known as “set” (i.e. participant emotional/cognitive/behavioral state/mindset and expectations just prior to psilocybin exposure) and “setting” (the physical environment in which the exposure occurs), the rate of adverse responses to classic psychedelic exposure dropped significantly (Metzner, Litwin, & Weil, 1965; Pahnke, 1969). Confirmation of the importance of context for optimizing the therapeutic benefit of psilocybin (and other psychedelics) comes from a meta-analysis of 23 controlled studies and provides a strong rationale for the use of the SaS in this protocol (Studerus, Gamma, Kometer, & Vollenweider, 2012).

By the mid-1960s, a set and setting approach had been widely accepted as including three components: 1) preparation prior to drug session; 2) drug session; and 3) post session meetings to integrate the psychedelic experience. In component 1, participants underwent pre-exposure preparation sessions designed to build rapport with the Facilitators who would be present during the drug exposure session and to identify personal themes and struggles that might be especially likely to impact the session experience. In component 2, the drug session itself was conducted by two Facilitators (typically a male and female dyad) who were present throughout the session. Sessions were typically conducted in a room designed to be quiet, comfortable, and aesthetically pleasing, and participants were encouraged to wear eyeshades and listen to a program of music on headphones during the drug exposure to aid them in focusing their attention inward. In component 3, participants engaged in a series of drug-free interview meetings of variable frequency, sometimes over a period of several weeks, to discuss their session experience thoroughly.

The SaS protocol proposed in the current study is in line with this 3-component model. A full and detailed description of information and instructions given during the study preparation, dosing, and integration sessions is provided in the *Usona Facilitator Training Manual* and in the study manual of procedures (MoP). The intervention protocol, for purposes of this research study, includes the period of participant preparation prior to drug administration, the 7-10 hour drug session, and the post-dose integration sessions to maximize participant safety and support. It is for this reason that eligibility verification is conducted prior to the preparatory sessions rather than immediately preceding the delivery of study medication (psilocybin vs. active placebo).

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of this study is to evaluate the potential efficacy of a single 25 mg oral dose of psilocybin for major depressive disorder (MDD) compared to an active placebo (niacin) in otherwise medically healthy participants ages 21 to 65, assessed as the difference between groups in changes in MADRS-assessed depressive symptoms from Baseline to Day 43 post-dose.

2.2 Secondary Objectives

The key secondary objective of this study is to evaluate the potential efficacy of a single 25 mg dose of psilocybin for MDD compared to an active placebo in medically healthy participants ages 21 to 65, measured as between-group difference in change in MADRS-assessed depressive symptoms from Baseline to Day 8 post-dose.

Additional secondary objectives are to evaluate between-group differences in:

- Change in Sheehan Disability Scale (SDS)-assessed functional disability status from Baseline to Day 43 post-dose
- Sustained depressive symptom response following dosing
- Sustained depressive symptom remission following dosing

2.3 Exploratory Objectives

Exploratory objectives of this study are to evaluate the potential efficacy of a single 25 mg oral dose of psilocybin for MDD compared to an active placebo in medically healthy participants between the ages of 21 and 65, measured as between-group differences in:

- Change in MADRS-assessed depressive symptoms from Baseline to post-dose Day 2, 15 and 29
- Change in Clinical Global Impression—Severity (CGI-S) score from Baseline to post-dose Day 8, 15, 29 and 43
- Change in Hamilton Anxiety Rating Scale (HAM-A)-assessed anxiety symptoms from Baseline to post-dose Day 8, 15, 29 and 43
- Change in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)-assessed health-related quality of life from Baseline to post-dose Day 8, 15, 29 and 43
- Change in SDS-assessed functional disability to post-dose Day 8, 15 and 29
- Degree of concordance between central-rated and computer-administered MADRS measures of depressive symptoms at Baseline and post-dose time points
- Change in Symptoms of Major Depressive Disorder Scale (SMDDS)-assessed depressive symptoms from Baseline to post-dose Day 8 and 43
- Change in SMDDS-assessed depressive symptoms from pre-dose Day 1 to post-dose Day 8 and 43
- Change in Oxford Depression Questionnaire (ODQ)-assessed depressive symptoms from Baseline to post-dose Day 43

2.4 Exploratory Mechanism-Based Objectives

Exploratory mechanism-based objectives of this study are to evaluate the potential impact of acute psychological effects of a single 25 mg dose of psilocybin on longer-term antidepressant effects in MDD compared to an active placebo in medically healthy participants ages 21 to 65, measured as between group differences in:

- 30-item Mystical Experience Questionnaire (MEQ-30) score reported post-dose
- Emotional Breakthrough Inventory (EBI) score reported post-dose
- Association between mystical-type experiences reported post-dose and longer-term changes in MADRS-assessed depressive symptoms
- Association between EBI-assessed emotional break through experiences reported post-dose and longer-term changes in MADRS-assessed depressive symptoms

2.5 Safety Objectives

The overall safety objective of this study is to evaluate a single 25 mg oral dose of psilocybin compared to an active placebo in incidence, severity and frequency of Adverse Events (AEs), Treatment Emergent AEs (TEAEs), Solicited AEs, and Serious Adverse Events (SAEs) before, during and after the dosing session and at all follow-up visits.

- 1) Period 1 (Screening Period): Screening through end of Baseline;
- 2) Period 2 (Preparation Period): Preparation until Randomization;
- 3) Period 3 (Dosing Period): Randomization through Day 9; and
- 4) Period 4 (Follow-up Period): Day 10 through Day 43

2.6 Specific Safety Monitoring Objectives

Safety will be continually evaluated by study staff through monitoring and assessment of AEs, vital signs, concomitant medication use, physical exams, safety labs, site rater administered measures, and integration with session Facilitators. The study will also assess abuse liability, including non-clinical, illicit use of psilocybin and other psychedelics and other illicit and non-prescribed drug use via the AUDIT and DUDIT, Timeline Followback, Substance Use Disorders module of the SCID-CT, participant self-report, and urine drug testing per the Schedule of Assessments ([Table 1](#)). Additionally, a Data and Safety Monitoring Board (DSMB) will review and oversee safety data.

Specific safety monitoring objectives in each of the study periods are as follows:

Period 1:

- Incidence of AEs by severity
- Incidence of AEs requiring medical attention
- Incidence of AEs requiring psychiatric attention
- Incidence of AEs leading to withdrawal from study
- Incidence of SAEs

- Incidence of new concomitant medications
- Incidence of self-report or urine toxicology identified illicit and non-prescribed drug use

Period 2:

- Incidence of AEs by severity
- Incidence of AEs requiring medical attention
- Incidence of AEs requiring psychiatric attention
- Incidence of AEs leading to termination from study
- Incidence of SAEs
- Incidence of new concomitant medications
- Incidence of self-report or urine toxicology identified illicit and non-prescribed drug use

Period 3:

Differences between the psilocybin and active placebo groups in:

- Incidence of AEs by severity
- Incidence of AEs requiring medical attention
- Incidence of AEs requiring psychiatric attention
- Incidence of AEs leading to termination from the study
- Incidence of TEAEs
- Incidence of TEAEs by severity
- Incidence of solicited AEs
- Incidence of solicited AEs by severity
- Incidence of SAEs
- Incidence of new concomitant medications
- Incidence of psychiatric concomitant medications
- Incidence of self-report or urine toxicology identified illicit and non-prescribed drug use
- Incidence of clinically significant abnormalities on safety laboratory assessments or physical examination

Period 4:

Differences between the psilocybin and active placebo groups in:

- Incidence of AEs by severity
- Incidence of AEs requiring medical attention
- Incidence of AEs requiring psychiatric attention
- Incidence of AEs leading to withdrawal from the study
- Incidence of TEAEs, to assess the relationship between study intervention and each occurrence of the relevant AE/SAE based on relative incidence in the psilocybin group
- Incidence of TEAEs by severity
- Incidence of solicited AEs
- Incidence of solicited AEs by severity

- Incidence of SAEs
- Incidence of new concomitant medications
- Incidence of psychiatric concomitant medications reported
- Incidence of self-report or urine toxicology identified illicit and non-prescribed drug use
- Incidence of clinically significant abnormalities on safety laboratory assessments or physical examination

2.7 Primary Study Endpoint

- Between-group difference in mean change of central rater Montgomery-Asberg Depression Rating Scale (MADRS) score from Baseline to post-dose Day 43

2.7.1 Justification for Primary Study Endpoint

The selection of Day 43 (week 6) as the primary study endpoint is consistent with standard practice in antidepressant trials. As the final time point in the current protocol it is also the most relevant for evaluating the persistence of benefit for the study drug vs niacin. In regards to the key secondary endpoint, as with other rapidly acting investigational antidepressant agents (e.g. ketamine), a single dose of psilocybin has shown to induce a large effect-size reduction in depressive symptoms within a day of administration in comparison to active placebo, with no further improvement in symptom scores seen at subsequent assessment points (i.e. at 2 weeks and 6 weeks post-intervention) (Ross et al., 2016). These findings demonstrate that an assessment at one week post-intervention will likely capture the entire antidepressant effect of psilocybin, both in comparison to active placebo and in comparison to baseline symptom score. Further support for the appropriateness of one week post-intervention as the key secondary study endpoint comes from the association of immediate (e.g. one day post-intervention) and longer-term (e.g. six weeks post-intervention) antidepressant responses to both psilocybin and niacin in the New York University (NYU) study of depressed/anxious patients with cancer. In that study reductions in Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) depression subscale scores between baseline and one day post-intervention showed very large effect size correlations with reductions in BDI and HADS depressive subscale scores between baseline and six weeks post-intervention (*unpublished data*), as shown in this table:

Instrument	Niacin	Psilocybin
HADS-Depression	.750 ($p = .002$)	.925 ($p = .000016$)
BDI	.863 ($p = .001$)	.877 ($p = .000082$)

The selection of the MADRS to assess the study's primary endpoint is consistent with it being the most commonly used assessment tool for assessment of primary endpoints in recent phase 3 antidepressant registration trials. This is consistent with data indicating that in comparison to the other historically-used instrument, the Hamilton Depression Rating Scale (HAM-D), the MADRS shows improved ability to capture meaningful clinical improvement in response to active antidepressants versus placebo (Carmody et al., 2006).

2.8 Secondary Study Endpoints

- Between-group difference in change in central rater MADRS score from Baseline to post-dose Day 8 (Key Secondary)
- Between-group difference in change in site rater administered SDS score from Baseline to post-dose Day 43
- Between-group difference in sustained depressive symptom response defined as a $\geq 50\%$ reduction from Baseline central rater MADRS score at the following post-dose assessments: Day 8, 15, 29 and 43
- Between-group difference in sustained depressive symptom remission defined as a central rater MADRS total score ≤ 10 at the following post-dose assessments: Day 8, 15, 29 and 43

2.9 Exploratory Study Endpoints

- Between-group difference in change in central rater MADRS score from Baseline to Day 2, 15 and 29 post-dose
- Between-group difference in change in central rater CGI-S score from Baseline to Day 8, 15, 29 and 43 post-dose
- Between-group difference in change in HAM-A score from Baseline to Day 8, 15, 29 and 43 post-dose
- Between-group difference in change in Q-LES-Q score from Baseline to Day 8, 15, 29 and 43 post-dose
- Between-group difference in change in site rater administered SDS score from Baseline to Day 8, 15, and 29 post-dose
- Degree of concordance between change in central rater MADRS score from Baseline to all post-dose assessments and computer-administered MADRS score over the same assessment period.
- Between-group difference in change in SMDDS score from Baseline to Day 8 and Day 43
- Between-group difference in change in SMDDS score from pre-dose Day 1 to post-dose Day 8 and 43
- Between-group difference in change in ODQ score from Baseline to Day 43

2.10 Exploratory Mechanism-Based Endpoints

- Between-group difference in post-dose 30-item MEQ-30 score
- Between-group difference in post-dose EBI score

2.11 Safety Endpoints

- Relative incidence of AEs by severity
- Relative incidence of TEAEs by severity
- Relative incidence of SAEs by severity
- Relative incidence of treatment-emergent concomitant medication use
- Relative incidence of solicited AEs by severity

- Relative incidence of clinically significant abnormalities and changes from Baseline in clinical laboratory values
- Relative incidence of clinically significant abnormalities and changes from Baseline in vital signs
- Relative incidence of clinically significant physical examination findings
- Relative incidence of self-report or urine toxicology identified illicit and non-prescribed drug use

2.12 Outcome Measures

See [Appendix B](#) for a table of clinical outcome assessments.

2.12.1 Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a 10-item depression rating scale developed in 1979 to be more sensitive to symptom changes induced by antidepressants than were currently available instruments (Montgomery & Asberg, 1979). The MADRS has been used for assessing primary outcomes in registration trials for new pharmacological agents for treating MDD, whether these agents are traditional monoamine modulators (e.g., vilazodone, vortioxetine) or agents with novel mechanisms of action (e.g., esketamine) (Daly et al., 2018). The MADRS includes questions on the following symptoms 1. Reported sadness 2. Apparent sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts. Items are scored via a clinical interview that progresses from more broadly phrased questions about symptoms to more detailed queries that allow a precise rating of severity. Items are rated to capture the patient's clinical state over the prior week. Each item yields a score of 0 to 6, and higher scores indicate more severe depression. The overall score ranges from 0 to 60. Various studies have suggested cut scores from < 9 to < 12 as a definition of remission. For the current study, remission will be defined as a score ≤ 10 .

To reduce the risk of functional unblinding during collection of the primary study outcome measure, MADRS assessments will be conducted by a blinded, remote and independent central rater. Central raters will be blinded to participant allocation, visit number (i.e. where in the study any given participant is for any given assessment), and the specifics of the protocol and study design.

At the site, the central-rated MADRS assessments will be conducted by telephone in a private room. Use of telephone/audio is the standard administration method recommended by Signant Health and has been selected instead of video for the following reasons: (1) it should be noted that rating certain items, such as *Apparent Sadness*, can reliably be administered by telephone (Hermens et al., 2006), and because it is based on the prior 7 days and not just the 20-30 minutes of the interview, visual inspection of the participant is not required; and (2) the rating without visual cues asks questions using a structured algorithm-driven process which assures high intra-rater reliability as well as high inter-rater reliability. Additionally, ratings made without visual cues are less prone to functional unblinding and are highly concordant with live ratings (K. A. Kobak, Williams, Jeglic, Salvucci, & Sharp, 2008). It is expected that the random assignment of blinded visits to central raters, and interference effects between visits from one respondent, will mitigate the possibility of voice recognition. Video recordings would greatly increase any

possible effect of unblinding the central raters. Most importantly, the study design compares drug placebo differences and there is no reason to believe any discrepancy would differentially impact the treatment groups.

In addition to the independent central-rater administered MADRS administration via telephone, to enhance quality control of the primary outcome instrument, each participant will complete a brief interactive, computer-administered MADRS on the dedicated study device. The computer-administered MADRS will involve a series of standardized queries and follow up questions with multiple-choice response options. This type of tandem assessment strategy is now frequently used in registration trials to enhance reliability of the data by screening out participants who are unable to provide consistent reports of their current depressive symptomatology. The tandem MADRS ratings also provide a quality metric that facilitates assessment of rater and site quality.

At Screening, the computer administered MADRS will be collected first, followed by the central rater administered MADRS. At Baseline and through the Day 43/ End of Study assessment, the central rater administered MADRS will come before the computer administered MADRS. The purpose of conducting the computer administered MADRS first at Screening is to assess eligibility early and eliminate further screening activities. The central rater assessment will be conducted first at later visits as it is the primary endpoint assessment.

MADRS item 10 inquires about suicidal ideation. A score of ≥ 5 suggests that a participant may be experiencing a level of active suicidal ideation that will require a clinical assessment, management and disposition.

The computer administered MADRS will be collected electronically [electronic Clinical Outcome Assessments (eCOA)] on a study specific tablet or computer. The central rater telephone MADRS will be collected using a Signant Health specific tablet or computer, with data entered in real time by the central rater.

2.12.2 Sheehan Disability Scale (SDS)

The SDS will be utilized to determine the impact of psilocybin vs. placebo on functional disability (psychosocial functioning). This will be an important secondary endpoint for the current study. The SDS is a composite of three self-rated items designed to measure the extent to which three major sectors in the patient's life are impaired by psychiatric symptoms, including depression (D. Sheehan, 1983; K. H. Sheehan & Sheehan, 2008). This scale has been used widely in psychopharmacology randomized controlled trials and has been accepted by the Food and Drug Administration (FDA) for functional disability labeling. The SDS uses visual-spatial, numeric, and verbal descriptive anchors simultaneously to assess disability across three domains: work, social life, and family life. The SDS was developed as an intervention outcome measure that would be sensitive to change and to drug placebo differences over time. The SDS asks patients to rate the extent to which his or her 1) work/school, 2) social life or leisure activities, and 3) home life or family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale. There are verbal descriptors for the points on the scale as well as numerical scores that provide more precise levels of the verbal descriptors. Typically, four scores are derived from the scale in research studies – one for each of the work, social life and family life disability measures and an aggregate total score of these three scores combined.

To limit missing data and ensure standardized administration, the SDS will be administered electronically in a clinician-rated format by trained site raters. The site rater administration will be important in limiting misinterpretation of the Work/school impairment item that could contribute to elevated rates of skipping out, which can also be completed in reference to school, unpaid or volunteer work, and may not immediately come to mind in a participant-reported format. As the scale cannot be modified, if a participant indicates that Item 1 (work/school) is not applicable, the reason that it is not applicable will be documented in the site rater notes, with data entered into the Signant Health system and integrated into the full study dataset.

2.12.3 Hamilton Anxiety Rating Scale (HAM-A)

The computer-administered form of the HAM-A (Kenneth A. Kobak, Reynolds, & Greist, 1993) is an anxiety rating scale designed to have high correspondence with the standard version of the HAM-A (HAMILTON, 1959). The computer-administered version consists of 153 questions that are scored to match the 14 items of the standard HAM-A: anxious mood, tension, fear, insomnia, intellectual (cognitive) symptoms, depressed mood, behavior at interview, somatic (sensory), cardiovascular, respiratory, gastrointestinal, genitourinary, autonomic and somatic (muscular) symptoms. Each scored symptom is rated from 0 (absent) to 4 (maximum severity). Total scores range from 0 to 56.

The HAM-A is a self-report instrument that will be collected electronically (eCOA) on a study specific tablet or computer and will involve a series of probe and follow up questions with multiple-choice response options.

2.12.4 Clinical Global Impression – Severity (CGI-S)

The CGI rating scales are measures of symptom severity, intervention response and the efficacy of interventions in intervention studies of patients with mental disorders (Guy, 1976). The CGI-S is a 7-point scale that requires the central rater to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Possible ratings are:

1. Normal, not at all ill
2. Borderline mentally ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most extremely ill patients

The same central rater (Signant Health) who conducted the MADRS will conduct the CGI-S using a Signant Health specific tablet or computer with data entered in real time by the central rater. Likewise, they will be blinded to the protocol, study design and time-point (i.e. where in the study protocol a participant is at any given assessment).

2.12.5 Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)

The Q-LES-Q is a 16-item self-report measure, will be used to evaluate intervention-related changes in quality of life (Endicott, Nee, Harrison, & Blumenthal, 1993). A total score is derived from summing the first 14 items on the scale, with the last two items serving as stand-alone queries. Total score ranges from 14 to 70. In addition to a total score, the total raw score can be transformed into a percentage maximum possible score using a standard formula. The Q-LES-Q-SF was designed specifically to assess quality of life in the context of psychiatric disease, and has been repeatedly shown to be sensitive to clinical improvements in intervention trials and to capture unique variance in outcomes when compared to depressive symptom scales alone (Stevanovic, 2011).

The Q-LES-Q is a self-report instrument that will be collected electronically (eCOA) on a study specific tablet or computer.

2.12.6 30-item Mystical Experience Questionnaire (MEQ-30)

The MEQ is a self-report measure developed to assess the effects of classic psychedelics in laboratory studies. It is based on Stace's conceptual framework of mystical experiences (Stace, 1960), and covers the major dimensions of classic mystical experience: unity, transcendence, noetic quality, sacredness, positive mood, and ineffability/paradoxicality. The MEQ has been administered in various forms in a number of studies over the past 50 or more years (Bogenschutz et al., 2015; Garcia-Romeu, Griffiths, & Johnson, 2015; R. Griffiths, Richards, Johnson, McCann, & Jesse, 2008; R. R. Griffiths et al., 2011; R. R. Griffiths et al., 2006; Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Maclean, Leoutsakos, Johnson, & Griffiths, 2012; Richards, 1975). Items on the questionnaire are rated on a 6-point scale, where 0= "None; not at all", 1= "So slight cannot decide", 2= "Slight", 3= "Moderate", 4= "Strong", and 5= "Extreme". A factor analysis conducted by MacLean et al. found that the most recent version of the MEQ, a revised 30 item (MEQ30), is a psychometrically sound instrument for assessing psychedelic-occasioned mystical experiences (Barrett & Griffiths, 2017; Maclean et al., 2012).

The MEQ-30 will be administered upon completion of the dosing session when all behavioral effects of the intervention have resolved. The MEQ-30 is a self-report instrument that will be collected electronically (eCOA) on a study specific tablet or computer at the site.

2.12.7 Emotional Breakthrough Inventory (EBI)

The EBI is a new 6-item scale developed by researchers at Imperial College London that assesses the presence and severity of emotionally challenging/distressing experiences that occur during a psychedelic experience. The scale utilizes visual analog responses captured on a line anchored by "not at all" on one end and "very much so" on the other. Experiences queried include 1) facing emotionally difficult feelings that are usually pushed aside; 2) experiencing a resolution of a personal conflict/trauma; 3) being able to explore challenging emotions and memories; 4) having an emotional breakthrough; 5) getting a sense of closure on an emotional problem, and 6) achieving an emotional release followed by a sense of relief.

The EBI will be administered upon completion of the dosing session when all behavioral effects of the intervention have resolved. The EBI is a self-report instrument that will be collected electronically (eCOA) on a study specific tablet or computer at the site.

2.12.8 Symptoms of Major Depressive Disorder Scale (SMDDS)

The SMDDS assesses participant-reported symptoms associated with MDD to be used as an exploratory outcome. This 16-item instrument has a 7-day recall period, and participants respond to each question using a rating scale between 0 (“Not at all” or “Never”) to 4 (“Extremely” or “Always”). The total score ranges from 0 to 60 with a higher score indicating more severe depressive symptomatology.

The SMDDS is a self-report instrument that will be collected at Baseline and on Days 1 (pre-dose), 8, and 43.

2.12.9 Oxford Depression Questionnaire (ODQ)

The Oxford Depression Questionnaire (ODQ) is a patient-centered, self-report measure of emotional symptoms present in patients treated with antidepressants. In particular, it is a clinical tool that can facilitate the identification of patients with the syndrome of emotional blunting that they attribute to the effect of their antidepressant medication. It can also be used in studies to advance understanding of the nature, causes and particularly the treatment of this phenomenon (Price, Cole, Doll, & Goodwin, 2012).

The ODQ is a 26-item patient self-report measure, spread over 3 sections and covering 4 dimensions of 1) not caring (NC), 2) emotional detachment (ED), 3) positive reduction (PR), and 4) general reduction (GR). Section 1 includes 12 items, three items from each of the 4 dimensions (NC, ED, PR and GR). Recall period is the last week. In Section 2 there are 8 items (2 from each of the four dimensions) comparing respondents’ experiences during the previous week with in comparison to their experiences before they developed their illness / problem. Section 3 addresses the extent to which participants attribute their emotional difficulties to their antidepressant, and the extent to which they would therefore be considered by participants to be “emotional side-effects”. It also addresses the possible impact of emotional side-effects on antidepressant adherence. For the purposes of this study the questionnaire will substitute “study medication” for antidepressant, as approved by the questionnaire’s author. Response options are based on 5-point Likert scale with a score applied to each response. Results can be presented on a dimension basis or summed to give an overall ODQ score. If required as an additional dimension “Antidepressant as cause (AC)” can also be scored.

The ODQ will be administered at Baseline and Day 43 (at Baseline Section 3 will not be completed per questionnaire instructions as it is a study requirement all participants be off antidepressants at this point: “*If you are not currently prescribed antidepressants for your illness / problem, please tick this box ☐ and do not answer any more questions.*”). The ODQ is a self-report instrument that will be collected electronically (eCOA) on a study specific tablet or computer.

2.13 Eligibility and Safety Measures

2.13.1 Structured Interview for DSM-5 Disorders-Clinical Trials Version (SCID-CT)

The Structured Interview for DSM Disorders (SCID) is a semi structured, clinician-administered diagnostic interview that will be administered at the screening visit. The SCID is a semi-structured interview for making the major DSM-5 Axis I diagnoses. The SCID is considered to be the gold standard semi-structured assessment instruments for clinical and personality disorders (Williams et al., 1992). This study will use the SCID-Clinical Trials Version (First, Williams, Spitzer, L., & Gibbon, 2007), which has been developed specifically for clinical trials. This version provides customizable indication-specific configurations of the modules, so it can be easily tailored for use in specific studies, including MDD.

A new version of the SCID, the SCID-CT, has been developed in conjunction with i3 Research specifically for clinical trials. It aims to retain the diagnostic accuracy of the SCID, while streamlining for efficiency and simpler navigation. It also provides customizable indication-specific configurations of the modules, so it can be easily tailored for use in specific studies. While the format of the SCID-CT has been simplified to make it easier to use, the study participant questions remain the same as those found in the SCID – Research Version (SCID-RV).

Modified features of the SCID-CT include:

- 1) Only essential elements for drug indications that incorporate typical inclusion and exclusion criteria are included.
- 2) Subtypes and specifiers have been eliminated.
- 3) Criteria ratings have been streamlined into a “-” and “+” format rather than “?” “1” “2” “3” used in the Schedule of Assessments.
- 4) The Overview has been abridged to entail clinical trial relevant questions only.

The SCID-CT will be collected on paper and administered by a site rater with experience in the diagnosis of mental health disorders. Training to enhance interrater reliability within and between sites will be provided by Signant Health.

The SCID-CT will be used at Screening to assess study eligibility. At Day 43/End of Study, if there is a concern that the participant has developed a potential substance or alcohol use disorder (based on results from Timeline Followback and investigator discretion), the Substance Use Disorders module of the SCID will be used to identify potential substance and alcohol use disorders that develop since dosing.

2.13.2 SCID-5-Personality Disorders (SCID-PD)

The SCID-PD (Association) is the updated version of the former Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). The SCID-PD assesses the 10 DSM-5 Personality Disorders across Clusters A, B, and C as well as Other Specified Personality Disorder. Designed to build rapport, the SCID-PD can be used to make personality disorder diagnoses, either categorically (present or absent) or dimensionally. The SCID-PD name reflects

the elimination of the multi-axial system in DSM-5. Although the DSM-IV Personality Disorder criteria are unchanged in DSM-5, the SCID-5-PD interview questions have been thoroughly reviewed and revised to optimally capture the construct embodied in the diagnostic criteria. The instrument assesses the DSM-5 criteria for each of the 10 personality disorders: Avoidant Personality Disorder, Dependent Personality Disorder, Obsessive-Compulsive Personality Disorder, Paranoid Personality Disorder, Schizotypal Personality Disorder, Schizoid Personality Disorder, Histrionic Personality Disorder, Narcissistic Personality Disorder, and Antisocial Personality Disorder. Administration of the SCID-PD will allow identification of exclusionary personality disorder (antisocial personality disorder) and an assessment of whether a personality disorder is a more primary problem than MDD.

Modules of the SCID-PD relevant for study inclusion/exclusion criteria will also be collected on paper and administered by qualified study personnel with experience in the diagnosis of mental health disorders. Training will be provided by Signant Health.

2.13.3 Drug History Questionnaire (DHQ)

The Drug History Questionnaire (Sobell, Kwan, & Sobell, 1995) is a one-page form that collects data for nine different drug classes: alcohol, cannabis, hallucinogens, depressants, inhalants, narcotics, stimulants, tranquilizers, and other drugs. For each drug class, the following information is collected: was the drug ever used and, if so: number of years used; total years used; injection drug use (Yes/No), year last used; and frequency of use in the past 6 months.

The DHQ will be collected at screening to assess prior lifetime illicit and non-prescribed drug use. The DHQ will be collected electronically (eCOA) on a study specific tablet or computer.

2.13.4 Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT is a ten-item assessment and respondents answer on a 5-point scale (0=Never or none, 4=Daily or greatest number) (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). The ninth item addresses occurrence of injury of self or other as a result of drinking and the tenth addresses others' concerns about the respondent's drinking, with only three responses provided (0=No, 2=Yes, but not during the last year, 3=Yes, during the last year). The measure can readily detect alcohol abuse disorders in a wide array of individuals (Allen, Litten, Fertig, & Babor, 1997).

At the Baseline visit the time frame covered by the AUDIT will be last year, consistent with scale instructions. At Day 43 the time frame will be specified as "since the last assessment." The AUDIT will be collected electronically (eCOA) on a study specific tablet or computer.

2.13.5 Drug Use Disorders Identification Test (DUDIT)

The DUDIT is an 11-item measure designed to assess presence of substance use disorders (Berman, Bergman, Palmstierna, & Schlyter, 2005). Responses to items are made on a 5-point scale with exact responses varying across questions. When present, use can be described in monthly or less than monthly versus four times a week or daily. A list of substances is provided at the end of the measure. The DUDIT is reliable, with a Cronbach's alpha of 0.80. When

compared with an interview based on ICD 10, the DUDIT had a sensitivity to detecting substance use disorders of 90% and a specificity of 80% (Berman et al., 2005). The English translation was developed from a Swedish-language original. Estimated time to complete is 2 to 4 minutes.

At the Baseline visit the time frame covered by the DUDIT will be last year, consistent with scale instructions. At Day 43 the time frame will be specified as “since the last assessment.” The DUDIT will be collected electronically (eCOA) on a study specific tablet or computer.

2.13.6 Timeline Followback (TLFB)

The Timeline Followback (Sobell & Sobell, 1992) is a widely used, calendar-based self-report measure used to assess frequency and quantity of alcohol (Carney, Tennen, Affleck, K Del Boca, & R Kranzler, 1998) and cannabis and other illicit substance use (Hjorthoj, Hjorthoj, & Nordentoft, 2012). It involves asking participants to retrospectively estimate their use for a period of time prior to the interview date. The instrument uses a visual calendar in which the respondent charts life events in order to enhance recall of alcohol and substance use. The TLFB can be administered by an interviewer, self-administered, or administered by computer. For this study, it will be administered by a site rater at the time of self-reported use and at the Day 43/ End of Study to assess use since dosing.

2.13.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS was created to provide a more exhaustive examination of suicidal ideation and history than is provided by other depression-related outcome measures. The C-SSRS rates an individual’s degree of suicidal ideation on a scale, ranging from “wish to be dead” to “active suicidal ideation with specific plan and intent.” Questions are phrased for use in an interview format. Each item queries how frequently participants have these thoughts, how long the thoughts last and whether the thoughts can be controlled. They are asked about deterrent factors, and for the reasons for thinking of suicide. They are asked about “Actual Attempt[s]”, which is a “potentially self-injurious act committed with at least some wish to die, as a result of act.”

Each of the following questions addresses a different component of the respondent’s suicide ideation severity:

Question 1: Wish to be dead

Question 2: Non-specific active suicidal thoughts

- If the respondent answers “Yes” to Question 2, he/she is instructed to answer Questions 3-5. If the respondent answers “No” to Question 2, he/she may proceed with the Suicidal Behavior section.

Question 3: Active suicidal ideation with any methods (not plan) without intent to act

Question 4: Active suicidal ideation with some intent to act, without specific plan

Question 5: Active suicidal ideation with specific plan and intent

The “Baseline-Screen” version of the scale will assess active suicidal ideation in the past 2 months and any suicidal behavior in the past 12 months as well as lifetime suicidal ideation/behavior.

The “Since Last Visit” version of the scale assesses suicidality since the patient’s last visit. The “Since Last Visit” version will be used for all assessments from Baseline through Day 43. The C-SSRS has been found to be reliable and valid in the identification of suicide risk in several research studies (James C. Mundt et al., 2010; J. C. Mundt et al., 2013; Posner et al., 2011).

A score of ≥ 4 or endorsement of any suicidal behavior item on the C-SSRS suggests that a participant may be experiencing a level of active suicidal behavior that will require a clinical assessment, management and disposition.

The C-SSRS will be collected electronically by a site rater using a study specific tablet or computer. It will be administered by study personnel qualified and trained to conduct the assessment.

2.13.8 Lifetime Illness Characteristic Questionnaire (LICQ)

The LICQ will collect data about the participant’s MDD history and the current episode and is a diagnostic tool relevant in the screening process. Administration of the LICQ is a two-part process to include a computer-assessment followed by review of the information by a central rater. First, participants will complete a computer-administered LICQ assessment at the screening visit prior to the site rater administered SCID, on a designated device provided to the site. Second, the participants’ diagnostic information, based on the responses to the computerized interview, will be reviewed by clinicians, and any uncertainty raised by the participant’s responses on the diagnostic interview or between the SCID-CT and the LICQ will be discussed with the PI or site rater in order to establish confidence in the diagnosis. The LICQ does not provide data that will be directly used to determine eligibility. Rather, it provides an overview of the participant’s history and current symptoms that can be used by clinicians to gain an overall impression of the likely suitability of an individual for study participation.

As the LICQ is a diagnostic tool, the central raters at Signant Health who are reviewing the assessment are not blinded (they are separate from the raters performing the blinded MADRS assessments). The LICQ is a self-report instrument that will be collected electronically (eCOA) on a study specific tablet or computer followed by review by clinicians at Signant Health.

2.13.9 Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ)

The ATRQ is a standard validated measure for assessing antidepressant treatment history and will be administered at screening. Although originally designed for self-report, in the current study it will be administered by a trained site rater to aid the potential participant in identifying all relevant details of past medication use. The ATRQ defines 8 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. It also provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants and allows for assessment of a range of other psychotropic agents used to augment antidepressants in individuals with depression. The ATRQ has shown excellent validity when compared to interview by medical facilitators (Chandler, Iosifescu, Pollack, Targum, & Fava, 2010) and has

been shown to perform as well as more complex and time-consuming treatment-history scoring methods (Hazari, Christmas, & Matthews, 2013).

The ATRQ will be collected on paper and administered by study personnel qualified and trained to conduct the assessment.

2.13.10 Family History Screen (FHS)

The FHS collects information on symptoms of 15 psychiatric disorders for participant's first-degree relatives, including biological parents, siblings and children (Milne et al., 2009). The form itself is not diagnostic but rather it asks about symptoms of a disorder; final determination will come from further discussion with the rater once an endorsement is made on the FHS. For this study it will be administered by a site rater at screening to assess for first-degree relatives with schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or Bipolar I Disorder.

The FHS will be collected on paper and administered by a site rater qualified and trained to conduct the assessment.

2.13.11 Questionnaire Order of Assessments

At all visits, starting at Baseline, the central rater MADRS interview will be conducted prior to all other outcome assessments, followed by additional central rater assessments, patient-reported outcome measures and site rater administered assessments. Specific order of outcome assessments is provided in the MoP.

2.13.12 Laboratory Assessments

The following laboratory assessments will be performed in this study: Complete Metabolic Panel (CMP), Complete Blood Count with Differential (CBC w/ Diff), Thyroid Stimulating Hormone (TSH), high-sensitivity C-reactive Protein (hs-CRP), Urinalysis, INR (screening only), Urine Drug Test (including Buprenorphine) and Pregnancy Testing. A review of the literature finds no prior studies that examined the impact of psilocybin on safety lab values. To address this gap in the literature, these labs will be collected at Screening, Baseline, Day 2, Day 8, and Day 43. These blood samples will be collected for safety purposes and for pharmacodynamic analyses such as the determination of the impact of pre-treatment levels of hs-CRP on placebo-adjusted antidepressant response to psilocybin, as have been noted for other serotonergic antidepressant agents (Jha et al., 2017; Uher et al., 2014). Blood samples will also be collected in PAXgene tubes (or functional equivalent) at each sampling timepoint (i.e., Screening, Baseline, Day 2, Day 8, and Day 43) and stored for potential future transcriptome analysis.

In addition, subject to a participant's provision of consent, a pharmacogenomic blood sample will be collected at one of the sampling timepoints (i.e., at Screening, Baseline, Day 2, Day 8, or Day 43) for storage and potential future analysis. Participants will be given the option to consent to pharmacogenomic sample collection, which will not be required for entry into the study, and only those participants providing informed consent will have such samples collected. Future

analysis of these pharmacogenomic samples may include (but is not limited to) whole genome sequencing (deoxyribonucleic acid (DNA)) analysis.

2.13.13 Physical Examinations

Physical examinations will be conducted at Screening and Baseline to confirm eligibility for the study and at Day 8 and Day 43 visits to examine health related physical changes. Additional physical exams may be administered depending on participant's signs and symptoms at the discretion of the investigator.

3 PROTOCOL DESIGN

3.1 Overall Study Design

Approximately 100 patients (males and females) ages 21 to 65 who, at Screening, meet DSM-5 criteria for MDD with a current depressive episode of at least a 60-day duration, a Screening MADRS score ≥ 28 and who meet all other inclusion/exclusion criteria at Baseline will be enrolled into the study and randomized with a 1-to-1 allocation under double-blind conditions to receive a single 25 mg oral dose of psilocybin or a single 100 mg oral dose of niacin. Niacin will serve as an active placebo that provides an acute physiological response (flushing) that may aid in blinding of intervention allocation. All randomized participants will be included in the intent-to-treat (ITT) sample that will provide data for testing primary, secondary and exploratory study endpoints.

Only participants who meet depressive symptom severity criteria and who do not show an unacceptably large degree of symptom improvement between the Screening visit and the Baseline assessment (indexed by $\leq 30\%$ improvement on both the central rater and computer MADRS assessments) will be eligible for randomization. In addition, at Screening and Baseline, only participants with a score difference ≤ 7 between the central rater and computer MADRS assessments will be eligible for randomization. A larger discrepancy has been associated with an exceptionally high placebo response in prior studies conducted by the study central rater vendor (*data on file*). In addition, inability to be consistent in response to the same questions likely identifies individuals not sufficiently capable of providing reliable responses.

Potential participants who meet all other entry criteria at Screening but who are taking an antidepressant or an antidepressant plus an augmenting agent (e.g., a second antidepressant, an atypical antipsychotic, lithium) will be eligible for continuation in the study but will enter a medication taper during which current psychotropic medications will be withdrawn under the supervision of a study psychiatric medical provider. Participants will be eligible to undergo the Baseline assessment at least 2 weeks after the last dose of the applicable medication.

Participants deemed eligible following successful completion of all screening assessments will complete central rater, site rater and self-report measures at Baseline for a final eligibility determination. Eligible participants at Baseline will undergo preparation sessions and be eligible for randomization on Dosing Day to receive either psilocybin or niacin active-placebo and will complete follow-up visits and assessments on study Day 2, 8, 15, 29 and 43 (within corresponding visit windows). Study outcome measures will assess depressive symptoms, clinical global functioning, functional disability, anxiety symptoms and health-related quality of life. Safety outcome measures will be collected at all assessment time points from the time of consent through the end of study.

To enhance participant safety, the current study does not propose to test psilocybin as a “context-less” pharmacological agent, but rather within a “set and setting” (SaS) protocol similar to the protocol that has been used in all modern studies of psilocybin in both diseased and normal healthy populations. The SaS protocol for this study includes: 1) a period of preparation with session Facilitators prior to dosing; 2) administration of study medications in an aesthetically pleasing room under the supervision of two Facilitators who are present throughout the session (with the

exception of short, temporary allowances for facilitator breaks; e.g. bathroom breaks); and 3) three post-dose integration sessions during which participants are encouraged to discuss their intervention experience with the Facilitators. The SaS will be identical for those randomized to psilocybin or niacin active placebo.

3.2 Justification for Selected Aspects of the Study Design

3.2.1 Use of a single psilocybin dose

Traditional psychotropic agents used to treat MDD (e.g. antidepressants) require continued administration for maintenance of clinical efficacy (Andrews, Kornstein, Halberstadt, Gardner, & Neale, 2011), and single doses of novel agents such as ketamine that produce an antidepressant effect that outlasts the medication's direct biological activity rarely induce a therapeutic response that lasts more than a week (McGirr et al., 2015). On the other hand, available evidence suggests that a single dose of psilocybin when administered under the SaS protocol produces an antidepressant effect durable enough to justify this treatment modality as a significant addition to the antidepressant armamentarium. For example, in a study conducted at Johns Hopkins University (Hopkins) (R. R. Griffiths et al., 2016), 24 participants with cancer and clinically significant depression (mean HAM-D score = 22.84 [0.97]) randomized to receive a single dose of psilocybin demonstrated remarkably high rates of symptomatic response (79%) and remission (71%) six months post-intervention without requiring additional pharmacologic intervention. A similarly high rate of response at 26 weeks post-intervention was seen in 11 participants randomized to psilocybin in the study of depression/anxiety in patients with cancer conducted at NYU (BDI response = 82%; HADS Depression response = 82%) (Ross et al., 2016). Finally, a 12 participant open trial of two doses of psilocybin separated by a week in otherwise medically healthy patients with TRD reported BDI response rates at 3 months post-intervention as 58% and 3 month post-intervention remission rates as 42% (Carhart-Harris et al., 2016). Taken together, these data suggest that clinically-meaningful antidepressant efficacy for single dose (or two doses with one being less than half the dose proposed for the current study) can be observed out to 6 months post-intervention in the context of cancer, and at least 3 months post-intervention in medically healthy individuals with MDD.

3.2.2 Psilocybin and Niacin Dosing

This study will compare the depression-relevant behavioral effects of a single 25 mg oral dose of psilocybin with a single 100 mg oral dose of a niacin active placebo. A 25 mg oral dose of psilocybin was selected based on data from an open trial of psilocybin in otherwise medically healthy patients with TRD showing that this dose produced a robust and sustained antidepressant response. Moreover, this dose is within range of the absolute dosages received in previous trials of single-dose psilocybin for depression and anxiety in patients with cancer (actual mean dose based on weight of patients at each site was 23.4 mg for the study conducted at Hopkins (Roland Griffiths, PhD, *personal communication*) and 21.4 mg for the study conducted at NYU (Steve Ross, MD, *personal communication*). Justification for a fixed dose, as opposed to a weight-based strategy, comes from data pooled from four studies (N = 141) in which participants of varying weight were administered 30 mg/70 kg psilocybin, and from data from six studies of individuals of varying weight who received a dose of 23 mg (N = 21) [Garcia-Romeu A, Johnson MW,

Barrett FS, Carbonaro TM, Griffiths RR. Psilocybin effects in humans: absolute vs. body weight adjusted dose, *in preparation*].

In both cases, no significant effect of weight was seen on any acute psychological effects of psilocybin, suggesting that a fixed-dose strategy should be as effective as weight-based dosing while significantly simplifying future medication delivery. Moreover, a fixed dose of 25 mg of psilocybin produced large effect size reductions in depressive symptoms in medically healthy patients with TRD, as described in [Section 3.2.1](#).

The selection of 100 mg as the dose for niacin is based on several factors. First, it is above the 75 mg dosage that reliably induces skin flushing that may provide a physiological effect to help blind the study (<https://articles.mercola.com/sites/articles/archive/2017/03/06/is-niacin-flush-dangerous.aspx>). Second, it is less likely to induce the severity of flushing that was frequently seen when a dose of 250 mg was used to blind the NYU phase 2 study of psilocybin in patients with cancer and depression/anxiety (Ross et al., 2016). This level of flushing produced uncomfortable physical sensations that might induce a dysphoric state that would artificially inflate psilocybin-placebo differences. In addition, the degree of flushing induced by a 250 mg dose was occasionally patently apparent to observers (i.e. Facilitators), which may have worked against its use as a blinded active placebo.

3.3 Planned Duration of Study

The planned maximum study duration for each participant will be approximately 12 weeks (87 days), with variation primarily dependent on the length of the screening period, the number of days between Baseline and dosing, and the visit windows provided for each post-dose assessment.

The screening period will last between 7 and 35 days to allow for scheduling and completion of all screening activities and to allow for medication taper, if indicated. As noted above, this time period will also allow for identification of participants who respond to study screening with a significant reduction in depression severity (i.e. likely placebo responders). Participants who enter the screening medication taper and require more than 35 days to discontinue their medication and meet the time period to be medication-free, will be re-screened when the medication-free period has been met. Participants who are re-screened will have a longer overall study duration.

The period between eligibility verification at the Baseline assessment and the dosing session will be a maximum of 7 days, with variation being dependent upon participant and research team scheduling needs. Approximately 6-8 hours of preparation will occur over a 1-6 day period following the Baseline assessment. The intervention session will occur following completion of these preparation sessions but no later than 7 days following Baseline.

The period between the dosing session and completion of the final post-dose assessment will be on average 6 weeks (43 days), with some variation allowed as a result of each post-dose session having a window for completion.

Figure 1: Summary of Events Flowchart

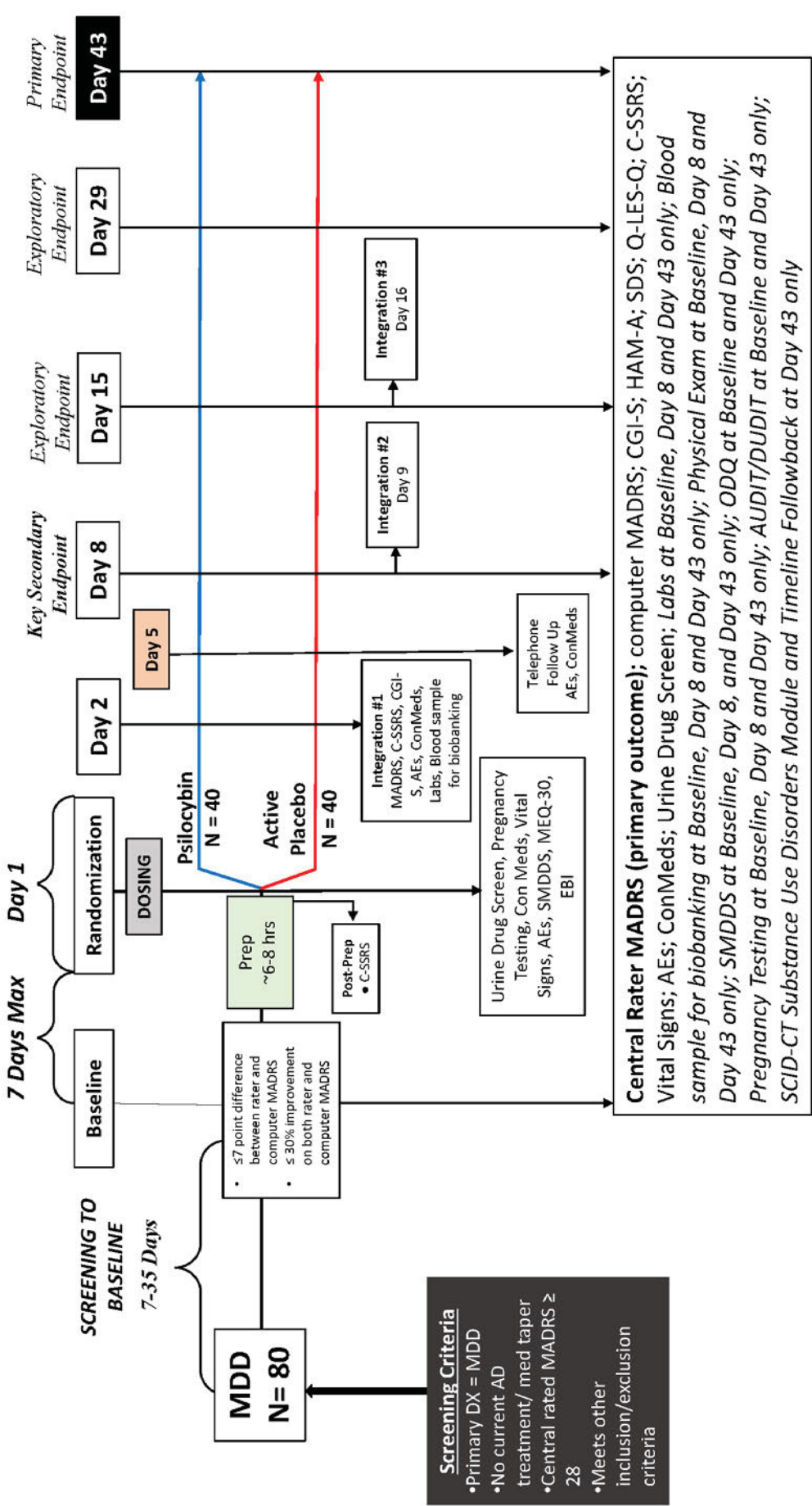


Figure 2: Study Diagram

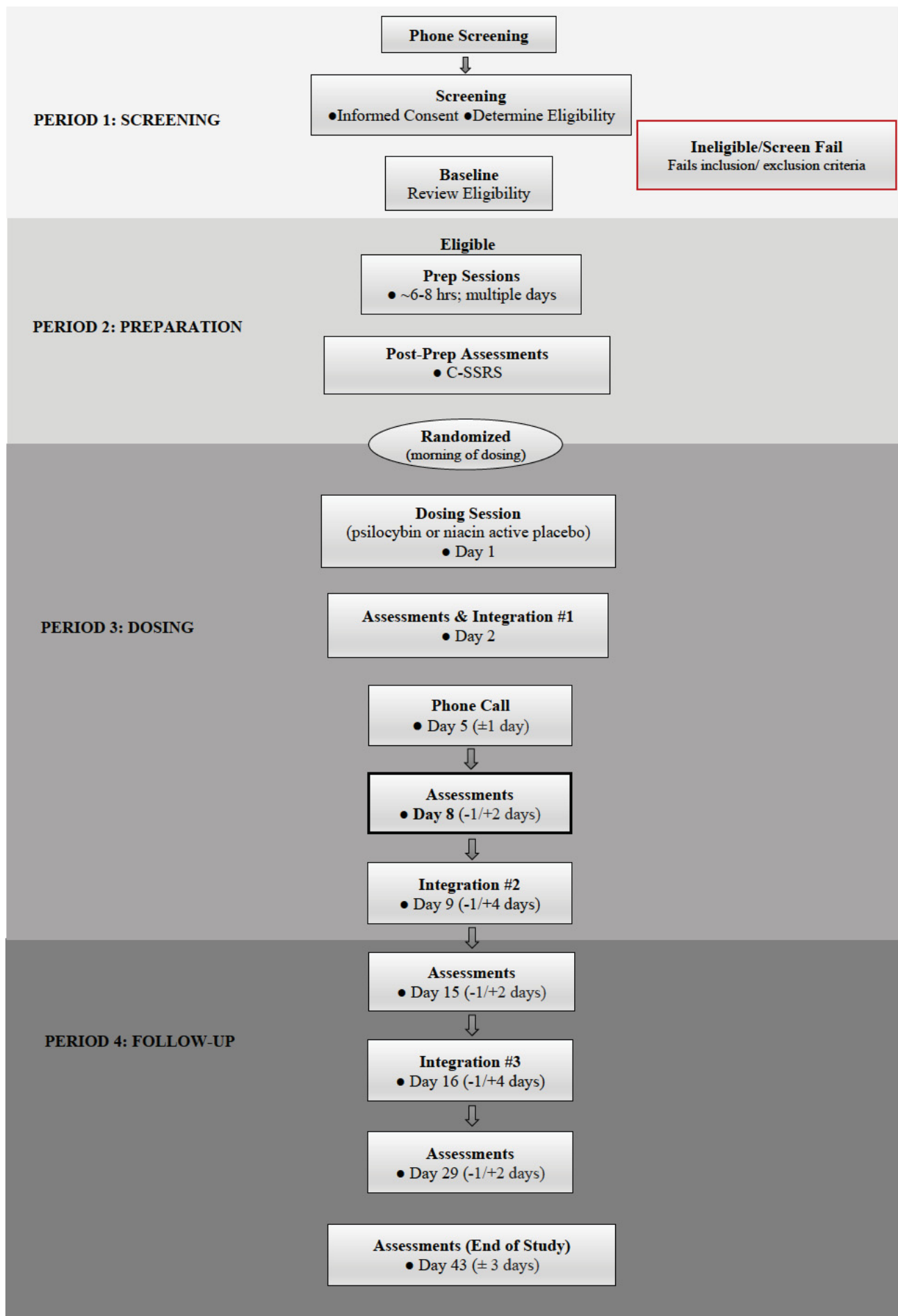


Table 1. Schedule of Assessments

Study Procedures & Measurements	Pre-Screen	SCREENING (7-35 days)		PREP		DOSE	FOLLOW UP				
		Screening	Baseline (max 7 days prior to dose)	Prep Sessions (1-6 days prior to dose)	Post-Prep Assessments (1-4 days prior to dose)	Day 1	Day 2	Day 5 Phone Call ±1 day	Day 8, 15, 29 -1/+2 days	Day 9, 16 -1/+4 days	Day 43 (End of Study) ± 3 days
Study Visit Number		00A	00B	00C	00D	01	02	03	04/06/08	05/07	09
Screen Form	X	X									
Informed Consent ²²		X ⁶									
Inclusion/Exclusion Verification ¹		X	X		X	X					
Demographics ²²		X									
Medical/ Psychiatric History ²²		X									
Physical Exam ²		X	X						X ⁷		X
Vital signs (BP, HR, Temp)		X	X			X ⁸	X		X		X
Height/Weight		X ⁹							X		X
12-lead ECG		X									
Laboratory Assessments											
Blood Sample for Biobanking and Future Analysis ²¹		X	X				X		X ⁷		X
CMP		X	X				X		X ⁷		X
CBC w/ Diff		X	X				X		X ⁷		X
TSH		X	X				X		X ⁷		X
hs-CRP		X	X				X		X ⁷		X
INR ³		X									
Urinalysis		X	X				X		X ⁷		X
Urine Drug Test		X	X			X ¹⁰			X		X
Urine Pregnancy Test (if applicable) ⁴		X	X			X ¹⁰			X ⁷		X
Questionnaires											
SCID-CT ²²		X									X ²⁰
SCID-PD ²²		X									
LICQ ²²		X									
ATRQ ²²		X									

Schedule of Assessments, page 2

Study Procedures & Measurements	Pre-Screen	SCREENING (7-35 days)		PREP		DOSE	FOLLOW UP				
		Screening	Baseline (max 7 days prior to dose)	Prep (1-6 days prior to dose)	Post-Prep Assessments (1-4 days prior to dose)		Day 2	Day 5 Phone Call ±1 day	Day 8, 15, 29 -1/+2 days	Day 9, 16 -1/+4 days	Day 43 (End of Study) ± 3 days
Study Visit Number		00A	00B	00C	00D	01	02	03	04/06/08	05/07	09
Family History Screen ²²		X									
MADRS ²²		X	X				X		X		X
DHQ ^{5,22}		X									
AUDIT ²²			X								X
DUDIT ²²			X								X
SMDDS ²²			X			X ¹⁰			X ¹¹		X
ODQ ²²			X								X
C-SRS ²²		X	X		X		X		X		X
HAM-A ²²			X						X		X
SDS			X						X		X
CGI-S ²²		X	X				X		X		X
Q-LES-Q ²²			X						X		X
Facilitator Dosing Monitoring Form						X ¹²					
MEQ-30						X ¹³					
EBI						X ¹³					
Timeline Followback ^{5,22}											X
Other Activities/ Assessments											
Medication Taper		X ¹⁴									
Preparatory/ Integrative Sessions				X ¹⁵			X ¹⁶			X ¹⁶	
Randomization						X ¹⁷					
Dosing (psilocybin or active placebo)						X					
Concomitant Medications ²²		X	X	X	X	X	X	X	X	X	X
Participant release evaluation						X ¹⁸					
Adverse Events ²²		X	X	X	X	X ¹⁹	X	X	X	X	X

- ¹ Inclusion/ Exclusion Verification will occur at Screening and Baseline; eligibility confirmation will be ongoing until dosing and will occur at post prep and prior to randomization;
- ² Complete physical exam conducted at Screening, Baseline, Day 8, and Day 43;
- ³ INR is collected to calculate Child-Pugh score;
- ⁴ All WOCBP who were assigned biological sex of female at birth, and have had no change in biological sex regardless of gender identification, will be required to undergo urine pregnancy testing; documentation of birth control method for all WOCBP will occur at screening and confirmed at each follow up visit;
- ⁵ The DHQ will assess lifetime psychedelic and other illicit and non-prescribed drug use at Screening (reassessed by self-report from Baseline to Randomization); all subsequent use starting with dosing will be assessed via the Timeline Followback at the time of self-reported use and at the Day 43/ End of Study visit;
- ⁶ Enrollment occurs at the time the informed consent form is signed;
- ⁷ Blood sample for biobanking and future analysis , CMP, CBC/ w Diff, TSH, hs-CRP, Urinalysis, physical exam and pregnancy testing will be done at Day 8 visit only and not the Day 15 or 29 visits.
- ⁸ Day 1 vital sign assessments will occur pre-dose; during the dosing session only BP and HR will be collected; BP, HR and temp will be collected at the end of dosing (7-hours);
- ⁹ Height collected at screening only;
- ¹⁰ Urine drug screen and pregnancy testing (if applicable) will occur prior to randomization, and completion of the SMDDS will occur prior to investigational drug administration;
- ¹¹ The SMDDS is collected at Day 8 only visit and not the Day 15 or 29 visits;
- ¹² The Facilitator Dosing Monitoring Form will be collected during dosing;
- ¹³ MEQ-30 and EBI are completed at the end of the dosing session;
- ¹⁴ Medication taper applies only to those who qualify;
- ¹⁵ Preparatory sessions can occur over multiple days consisting of at least one in-person preparatory session. Additional preparatory sessions may be conducted remotely, if necessary ;
- ¹⁶ Integration Session #1 on Day 2 should occur after all Day 2 assessments have been completed; Day 9 (Integration Session #2) should occur after all Day 8 activities have been completed; Day 16 (Integration Session #3) should occur after all Day 15 activities have been completed. Integration sessions may be completed remotely, if necessary;
- ¹⁷ Eligibility will be verified prior to Randomization, including confirmation of negative urine drug and pregnancy testing (for WOCBP only);
- ¹⁸ To assess readiness for release from the research facility following the dosing session, study staff will evaluate medical and psychiatric functioning;
- ¹⁹ Collection of AEs includes solicited AEs at every visit;
- ²⁰ At Day 43/ End of Study, only the Substance Use Disorders module of the SCID-CT will be completed, if warranted and based on results of the TLFB and investigator discretion
- ²¹ Blood samples will be collected in PAXgene tubes (or functional equivalent) at each sampling timepoint (i.e., Screening, Baseline, Day 2, Day 8, and Day 43) and stored for potential future transcriptome analysis. A pharmacogenomic blood sample will be collected only once and can be collected at any timepoint that involves a blood draw (i.e., Screening, Baseline, Day 2, Day 8, or Day 43). Participant must provide optional informed consent to enable collection of a pharmacogenomic blood sample and may opt out of providing such a sample during the informed consent process. Future analysis of these pharmacogenomic samples may include (but is not limited to) whole genome sequencing DNA analysis.
- ²² Procedure or measurement may be conducted remotely, if necessary.

4 PARTICIPANT POPULATION

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

Individuals eligible to be randomized in this protocol are those who meet *all* of the following criteria:

1. Are 21 to 65 years old at the time of written informed consent at the Screening visit
2. Are able to read, speak, and understand English
3. Are able and willing to adhere to study requirements, including attending all study visits, preparatory and follow-up sessions, and completing all study evaluations
4. Are able to swallow capsules
5. Women of childbearing potential (WOCBP) must agree to practice an effective means of birth control throughout the duration of the study, from Screening through the Day 43 assessment (see [Section 15](#) Pregnancy for a definition of WOCBP)
6. Meet DSM-5 criteria for a diagnosis of major depressive disorder and are currently experiencing a major depressive episode of at least a 60-day duration at the time of the Screening
7. Have sustained moderate-severe depression symptoms at Screening and Baseline, as defined by a Screening MADRS total score ≥ 28 and $\leq 30\%$ improvement (i.e. decrease) in MADRS total score from Screening to Baseline on both the central rater and computer assessments
8. Central rater MADRS and computer administered MADRS total scores show ≤ 7 point difference between scores at both Screening and Baseline
9. Have an identified support person
 - a. Agree to be accompanied home (or to an otherwise safe destination) by the support person, or another responsible party, following dosing

4.1.2 Exclusion Criteria

Individuals not eligible to be randomized in this protocol are those who meet *any* of the following criteria:

1. Women who are pregnant, as indicated by a positive urine pregnancy test at Screening or Baseline. Women who intend to become pregnant during the study or who are currently nursing.
2. Unwilling or unable to discontinue formal psychotherapy ([Section 4.2.2](#))
3. Unwilling to discontinue any current prescription or supplemental psychotropic agents (including trazodone for sleep) or are unable according to [Section 4.2.1 Medication Taper](#)
 - o Note: Benzodiazepine medications and non-benzodiazepine sleeping medications will be allowed to continue through the study period for participants who have been on a stable dose of such a medicine for at least 6 weeks prior to Screening.
4. Have previously received the following non-medication treatments:
 - a. deep brain stimulation (DBS)
 - b. vagus nerve stimulation (VNS)

5. Currently receiving electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)
 - Note: Previous treatment with ECT or TMS is allowed as long as last treatment was ≥ 90 days from the time of Screening
6. Unable or unwilling to discontinue any current medications having a primary centrally-acting serotonergic effect, including monoamine oxidase inhibitors (MAOIs) or dopaminergic antagonists
 - Note: Any prohibited agents must have been stopped at least 5x the elimination half-life of the specific drug at the time of Baseline. See [Appendix A](#) for a full list of prohibited medications.
7. Unable or unwilling to discontinue any current medications that are known uridine diphosphate (UDP) or glucuronosyltransferase (UGT) enzyme modulators, such as valproate
 - Note: Any prohibited agents must have been stopped at least 5x the elimination half-life of the specific drug at the time of Baseline. See [Appendix A](#) for a full list of prohibited medications.
8. Report the following psychedelic substances use:
 - a. Have used a psychedelic substance in the previous 5 years; or
 - b. Have used psychedelic substances > 10 times in their lifetime
 - Note: Psychedelic substances include psilocybin, Lysergic acid diethylamide (LSD), mescaline (and natural products containing mescaline including peyote and San Pedro cactus), N,N-Dimethyltryptamine (DMT), natural products containing DMT including ayahuasca and 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT), ibogaine, 2C compounds, 3,4-methylenedioxy-methamphetamine (MDMA), methylone or other psychedelics.
9. Have the following cardiovascular conditions:
 - a. coronary artery disease, congenital long QT syndrome (prior diagnosis), cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction (prior diagnosis);
 - b. tachycardia (defined as heart rate > 100 beats per minute);
 - c. a clinically significant Screening ECG abnormality (e.g., atrial fibrillation);
 - Note: A QTcF interval > 450 milliseconds is considered a clinically significant ECG abnormality
 - d. artificial heart valve; or
 - e. any other significant current or history of cardiovascular condition, based on the clinical judgment of study physician, that would make a participant unsuitable for the study
10. At Screening or Baseline have elevated blood pressure as defined as:
 - a. Screening blood pressure SBP > 135 mmHg or DBP > 85 mmHg on three separate readings; or
 - b. Baseline blood pressure SBP > 140 mmHg or DBP > 90 mmHg on three separate readings
 - Note: Please see justification for blood pressure parameters in [Section 4.2.8](#)
11. Have a history of stroke or Transient Ischemic Attack (TIA)
12. Have moderate to severe hepatic impairment, as indexed by a Child-Pugh score ≥ 7
13. Have epilepsy

14. Have insulin-dependent diabetes
 - Note: Participants who are taking oral hypoglycemic agent and have a history of hypoglycemia requiring medical intervention will be excluded
15. Are unable or unwilling to adhere to the following medication requirements:
 - a. Agree to suspend sildenafil (Viagra®), tadalafil, or similar medications at least 72 hours prior to dosing
 - b. If taking any supplement containing >20 mg of niacin, agrees to suspend use for at least five days prior to dosing and for the duration of the study
16. Have a positive urine drug test including Amphetamines, Barbiturates, Buprenorphine, Benzodiazepines, Cocaine, Cannabis, Methamphetamine, MDMA, Methadone, Opiates (Morphine, Oxycodone), Phencyclidine (PCP), and Tetrahydrocannabinol (THC).

Exceptions are made for prescribed Benzodiazepines (stable dose for sleep or anxiety).

 - Note: Prescribed benzodiazepine medications and non-benzodiazepine sleeping medications will be allowed to continue through the study period for participants who have been on a stable dose of such a medicine for at least 6 weeks prior to Screening, as determined during review of concomitant medications.
 - Note: Participants using cannabis, including legal cannabis, for any purposes must agree to refrain from use beginning at Screening, as confirmed with a negative Baseline drug test, and through to the end of the study.
 - Note: Participants who are taking prescription maintenance methadone or buprenorphine naloxone will be excluded.
 - Note: Prescription opiates must have been stopped at least 5x the elimination half-life of the specific drug at the time of dosing, as confirmed with a negative urine drug screen on Day 1 (prior to dosing). They can resume use following the Integration Session # 1 the day after dosing.
 - Note: Participants using prescribed psychostimulants (amphetamines and Ritalin), must agree to refrain from use two weeks prior to baseline visit, as confirmed with a negative Baseline drug test, and through to the end of the study.
 - Note: Participants using prescribed trazodone for sleep (at any dose) must agree to refrain from use two weeks prior to baseline visit and through to the end of the study.
17. Nicotine dependence that would disallow an individual to be nicotine free for the 7-10 hours during the dosing period
18. Meet DSM-5 criteria for schizophrenia spectrum or other psychotic disorders, including MDD with psychotic features (except substance/medication-induced or due to another medical condition), or Bipolar I or Bipolar II Disorder
 - Note: Participants with any lifetime diagnosis of schizophrenia spectrum or other psychotic disorders will be excluded
19. Meet DSM-5 criteria for antisocial personality disorder
20. Meet DSM-5 criteria for a moderate or severe alcohol or drug use disorder (excluding caffeine)
 - Note: Participants with a diagnosis of alcohol or drug use disorder within the past 12 months will be excluded
21. Have presence of any psychiatric condition or symptom judged by the PI (or designee) to be a more significant clinical problem than MDD for the participant, including a DSM-5 personality disorder

22. Have a first-degree relative with schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or Bipolar I Disorder
23. Have a psychiatric condition judged to be incompatible with establishment of rapport with the Facilitators or safe exposure to psilocybin
24. Report the following suicidal ideation or suicidal thoughts defined as:
 - a. Answer 'Yes' to C-SSRS Suicidal Ideation items 4 or 5 within the last 2 months at Screening or "since last visit" at Baseline;
 - b. Report having had any C-SSRS Suicidal Behavior item within the past 12 months at Screening or "since last visit" at Baseline, as defined by 'Yes' to any of the following on the C-SSRS: actual attempt, interrupted attempt, aborted attempt, or preparatory acts; or
 - c. Have a score of ≥ 5 on Item 10 (suicidal thoughts) of the central-rater or computer administered MADRS at Screening or Baseline; or
 - d. Have any suicidal ideation or thoughts, in the opinion of the study physician or PI, that presents a serious risk of suicidal or self-injurious behavior at any time prior to randomization
25. Have any suicidal ideation or thoughts, in the opinion of the study physician or PI, that presents a serious risk of suicidal or self-injurious behavior
26. Have any physical or psychological symptom, medication or other relevant finding prior to randomization, based on the clinical judgment of clinical/medical study personnel, that would make a participant unsuitable for the study.
27. Have an allergy or intolerance to any of the materials contained in either drug product

4.2 Justification for Inclusion/Exclusion Criteria

Provided below is a justification for criteria that are either not self-evident or differ in some way from standard practice in clinical trials in patients with MDD.

4.2.1 Medication Taper

The current study is designed to evaluate psilocybin as monotherapy for MDD, it is therefore important that individuals who otherwise qualify for study entry but who are currently receiving psychotropics, from which they do not appear to be benefitting based on the continued presence of significant depressive symptoms at Screening, be discontinued from these agents to participate in the study. Only individuals taking antidepressants who meet symptom severity criteria at Screening and endorse that the antidepressant they are taking is not providing benefit will be eligible. Any participant who believes he/she is being helped by the antidepressant, even if he/she endorses significant depressive symptoms, will not be eligible. In addition to the requirement to discontinue antidepressants to allow for an accurate assessment of the potential of psilocybin as monotherapy for depression, it should be noted that a strong rationale for not continuing these agents in a trial of psilocybin comes from evidence that antidepressants attenuate the types of behavioral responses to psychedelics that are linked to their antidepressant effect (Bonson, Buckholtz, & Murphy, 1996). Potential participants who have been on a stable dose of a benzodiazepine or a non-benzodiazepine sleeping agent for at least 6 weeks will be allowed to continue these medications on this fixed dose throughout the study period. Participants will be required to have taken their last antidepressant dose

at least 14 days prior to baseline. Details of the medication taper requirements are specified in the MoP.

4.2.2 Outside Psychotherapy

Participants will only be eligible for study enrollment if they agree and are judged able, from a safety perspective, based on the opinion of a study psychiatrist, to suspend any ongoing outside psychotherapy for the duration of study involvement. The rationale for suspending outside therapy is to allow for adequate evaluation of the study intervention. Suspending outside psychotherapy for the duration of the study is similar to the need for participants not to be taking outside psychotropic medications (e.g. antidepressants) during the study period. As with continuing pre-existing antidepressant medications, allowing participants to continue pre-existing outside psychotherapy would potentially confound the ability to unambiguously interpret study findings regarding whether monotherapy with psilocybin delivered in a therapeutic context shows an antidepressant effect when compared to placebo. This is true for several reasons. First and foremost, continuance of outside psychotherapy would not be “per protocol” and hence would not be standardized, nor would it be randomized, leading to the possibility of it being unequally distributed across groups. Moreover, it is completely unknown whether outside psychotherapy would potentiate or diminish antidepressant responses to psilocybin.

4.2.3 Benzodiazepines

Benzodiazepine medications and non-benzodiazepine sleeping medications will be allowed for participants who have been on a stable dose of such a medicine for at least 6 weeks prior to Screening. These medications are allowed because they have no psychotropic effects that might confound any potential differential antidepressant signal from the psilocybin vs. niacin placebo. On the other hand, requiring discontinuation of these sleeping agents prior to study drug dosing would likely disrupt stable sleep patterns that were part of the pre-treatment depressive symptom profile, and by doing this might interfere with potential antidepressant signals from the study drugs. Because these agents are used at bedtime, they will be out of participants’ systems prior to study drug dosing and thus should not interfere with either psychodynamic or pharmacokinetic properties of psilocybin.

4.2.4 Age range

The age range for the current study is typical for most antidepressant studies, with enrollment limited to individuals 21 years of age and older, but not older than 65 years. The rationale for excluding individuals with MDD younger than 21 is that they are at an increased risk of demonstrating a bipolar disease course with the passage of time and bipolar disease is believed to be contraindicated for the use of psilocybin (Moreno et al., 2012). There are no data to support the use of psilocybin in patients with bipolar disorder, nor data on how likely psilocybin would be to induce a manic episode in patients with a bipolar diathesis. In addition to this particular concern regarding incipient or misdiagnosed bipolar disorder in those younger than 21, individuals in this age group are in general at increased risk for adverse psychological reactions to antidepressants, as demonstrated by the black box warning for increased risk of suicidal thoughts and actions (<https://www.nimh.nih.gov/health/topics/child-and-adolescent-mental->

[health/antidepressant-medications-for-children-and-adolescents-information-for-parents-and-caregivers.shtml](#)).

This study will also exclude individuals older than 65 years of age. In addition, as with individuals younger than 21, older adults often differ from younger adults in factors associated with their depression and in their intervention response. For example, depression in older adults, especially when it is new onset, is significantly associated with the subsequent development of dementia (Alexopoulos, Young, & Meyers, 1993). And studies suggest that older adults are less likely than younger adults to respond to pharmacological treatments for MDD when depression is associated with brain changes also associated with dementia (Hsieh et al., 2002; Kalayam & Alexopoulos, 1999).

Additionally, over the course of its long-term clinical development phase, over a thousand participants have received psilocybin under controlled conditions in clinical settings for various indications (including healthy control subjects), with subsequent results published in peer-reviewed journals (Rucker, Iliff, & Nutt, 2017). The modern-day trials, enrolling approximately 165 adult participants, include open-label, dose-escalating studies, as well as randomized, double-blind placebo-controlled trials, and enrolled both healthy volunteers and various subpopulations with differing indications (Carhart-Harris et al., 2016; R. R. Griffiths et al., 2016; Ross et al., 2016). Multiple ongoing studies are continuing this exploration. All these studies had or currently have approval to enroll participants > 55 years (age ranges from 18-80 years). Furthermore, of the approximate 165 participants receiving study drugs in completed trials, 73 adult participants were > 55 years (Roland Griffiths, PhD; Matthew Johnson, PhD; Robin Carhart-Harris, PhD; Francisco Moreno, MD, Paul Hutson, PharmD; Stephen Ross, MD; Charles Grob, MD, *personal communication*). To date, no Serious Adverse Events attributed to the study drug were reported for any participant in these trials, regardless of age.

For these reasons, selecting the 21-65 year age range maximizes the generalizability of any potential positive findings while reducing risk and constraining biological/phenomenological variance that might decrease the power to detect clinically-relevant effects. Should results from the proposed study be promising, separate trials of psilocybin intervention in younger adult and geriatric populations would be warranted.

4.2.5 Medically Healthy Participants

The current study will enroll participants in good general overall medical health. While this somewhat limits the potential generalizability of any positive findings given the high comorbidity between mood disorders and medical disease, there are two primary reasons for choosing this strategy. First, medically-ill participants often have complex patterns of depressive pathogenesis born of the psychological stress of serious disease, but also likely from the direct physiological effects of the disease state itself, most notably the chronic immune activation that accompanies a wide range of medical illnesses (Raison, Capuron, & Miller, 2006). Given this,

separate studies are indicated to examine the potential antidepressant effects of psilocybin in patients with MDD and significant medical comorbidity.

4.2.6 Psychiatric Symptoms

Study inclusion/exclusion criteria include several exclusions related to psychiatric symptoms and conditions. Participants with active suicidal ideation with intent to act are excluded because these individuals require immediate psychiatric intervention with currently approved therapeutic modalities. The safe study of such individuals would require an inpatient setting and the current study will be conducted on an out-patient basis. Similarly, individuals with a history of medically-significant suicide attempt will be excluded given evidence that a recent history of suicide attempts increases the short-term risk for subsequent suicide attempts.

Individuals who are experiencing depression in the context of conditions characterized by a heightened risk for psychotic features, including schizophrenia and bipolar I and II disorder, are also excluded, including individuals with first-degree relatives with these conditions. These exclusions are based on the fact that not enough is known regarding the risks of a psychedelic experience in individuals with a vulnerability to psychosis to justify their inclusion in the current study. At the least, such individuals might have experiences occasioned by psilocybin that would differ markedly in their character and effects from experiences that would be more typical for individuals without psychosis risk.

As is common practice in phase 2 studies of new antidepressant modalities, individuals with active drug/alcohol abuse are excluded, as are those who have only recently achieved sobriety. Justification for these exclusions comes from evidence that antidepressant treatments are less effective in those who are actively abusing drugs/alcohol and from the fact that relapse rates are high during early sobriety, increasing the risk of a return to substance use during the study.

Because psilocybin administered under the SaS requires the development of rapport between participant and his/her intervention Facilitators, participants will be excluded prior to intervention if it is judged by the Facilitators (with agreement from a study clinician) that a given participant is not demonstrating a minimal degree of involvement/engagement with the intervention team.

Also, because this study focuses on MDD, participants with comorbid psychiatric conditions (e.g., obsessive-compulsive disorder, panic disorder) that are judged at Screening to be a more significant source of distress/impairment than the MDD will be excluded from study participation. Comorbid psychiatric disorders other than those specifically disallowed (i.e. psychotic disorders, bipolar I and II disorder, antisocial personality disorder) will be allowed if it is determined based on assessment at Screening that the participant's primary condition is MDD.

4.2.7 Medication Exclusions

In addition to these medical and psychiatric inclusion/exclusion criteria, participants will be required to abstain from medications/supplements that might interact with, or impact the experience of, psilocybin administration as listed in [Appendix A](#). This strategy is proposed both

to enhance safety (i.e. by limiting co-exposure to medications that might increase potential serotonin-related side effects of psilocybin) and to reduce biological heterogeneity of participants entering the intervention session.

4.2.8 Blood Pressure

The Screening and Baseline blood pressure criteria are in place for both safety and feasibility reasons. First, the American College of Cardiology and American Heart Association recently lowered their criteria for Stage 1 hypertension from SBP140 mmHg/ DBP 90 mmHg to SBP 130mmHg/DBP 80 mmHg, citing strong observational data to support this change (Whelton et al., 2018). By lowering the Screening BP criteria to SBP > 135 mmHg or DBP > 85 mmHg, the study will in effect recruit a healthier population that is at less risk for cardiovascular events. Second, due to the nature of the study, it is likely that some percentage of participants will present on the dosing day with vital signs elevated above Baseline values due to anxiety over the upcoming procedure (i.e. “white coat syndrome”). By reducing the Screening criteria to 135/85 mmHg, it is expected that the number of participants who fail to meet the dosing day (pre-dose) BP criteria of <140/90 mmHg due to elevated BP resulting from anxiety will be reduced. This change will significantly reduce the time burden and psychological stress on participants who would otherwise qualify but fail to meet BP criteria on the dosing day. Importantly, by setting more stringent BP parameters at screening we will also reduce the number of participants who will unnecessarily taper off from psychotropic agents and psychotherapy prior to dosing day should they be discontinued due to “white coat syndrome” elevation of BP on dosing day.

5 SCREENING PROCESS AND PROCEDURES

Study screening procedures and their timing are summarized in the Schedule of Assessments ([Table 1](#)) and full details are provided in the MoP. Participants will be provided with visit reminders. Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

5.1 Recruitment

Participants for the study will be recruited from the following sources: 1) a study specific website (see [Section 5.1.1](#)), 2) relevant clinical programs at each participating institution (e.g., departments of psychiatry, family medicine, etc.); 3) via advertisements on the web, in local print and radio and via flyers posted in relevant locations in the metropolitan areas in which the study will occur; and 4) via relevant national clinician-focused listservs and patient-advocate listservs. All advertisements, flyers and notices on listservs will be approved by all relevant IRBs prior to posting. As this study will require intensive study recruitment measures and new and various recruitment opportunities are found often, there may be instances of recruitment which do not fall under the above categories. However, prior to initiation of any recruitment activities, approval will be obtained from all relevant IRBs with IRB approved recruitment language/text.

5.1.1 Study Recruitment Website and Pre-Screener Questionnaire

A clinical research recruitment website will serve as the anchor for Usona's digital patient recruitment efforts and as the hub for study digital recruitment activities. The website contains basic educational content about clinical trials, depression and psilocybin. The study profile page provides key study details for prospective participants. Study profile page visitors who are interested in participating in the study may complete an eligibility pre-screener questionnaire.

Pre-Screener Questionnaire

The pre-screener includes questions regarding demographics and availability, medical and mental health questions, and prior psychedelic and other illicit drug use. It also includes a waiver of documentation of consent as it does not present more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context. During the pre-screener, participants will be informed, via the website, that answering questions is voluntary and that any information shared will be kept confidential. Identifiable contact information in the Rebar system will be encrypted.

Approval of the Sponsor's study recruitment website will fall under the purview of a central IRB, whereas each site will obtain institutional IRB approval for site specific recruitment activities.

5.2 Telephone Screen

Prospective participants will be prescreened by telephone at each participating institution, according to a local IRB-approved script, to learn if they meet basic eligibility criteria. The Telephone Screen will include questions similar to the pre-screener regarding demographics and availability, medical and mental health questions, and prior psychedelic and other illicit drug use. If a potential participant prefers, the telephone screen questions can be asked in person.

If at any time during the telephone screen process a potential participant discloses suicidal ideation, he or she will be immediately referred to a suicide crisis line or encouraged to call 911.

If the initial telephone screen suggests that the participant is eligible, a Screening visit will be scheduled. If the participant does not qualify or decides not to participate the reason will be documented in the Electronic Data Capture (EDC) system with all identifiable information encrypted.

Telephone Screen information will be verified at the Screening visit prior to written informed consent.

5.2.1 Telephone Screen Waiver of Documentation of Informed Consent

The Telephone Screen will include a waiver of documentation of consent as the Telephone Screen does not present more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context. During the telephone screen, staff will indicate that answering questions is voluntary, identifiable contact information in the EDC system will be encrypted. If a potential participant is deemed ineligible based on the telephone screen, their information will remain encrypted.

5.3 Written Informed Consent

For this trial, written informed consent will occur at the initial Screening visit. Study participants will be considered enrolled in the study when they provide written informed consent. All individuals who sign an ICF will be assigned a participant ID number in the EDC, which will be assigned sequentially. Written informed consent will be obtained from all participants before undergoing any study procedures. Prisoners, pregnant women and mentally impaired persons will not be included. Competent persons meeting other eligibility criteria will be welcomed, regardless of race, gender, ethnicity, religion or socioeconomic status. Additionally, students, employees, patients or family members affiliated with the PI(s) will not be enrolled, and family members of any study team member will be prohibited from participating in this study.

The following consent process will be adhered to for each participant:

- The PI or a qualified representative will explain the screening process and nature of the study to the participant and answer all questions.
- Participants must be informed that their participation is voluntary and that he/she may withdraw from the study at any time, for any reason.
- Participants will be provided adequate time for review and discussion prior to his/her making a decision about participation in the study, including the option to take the information home to discuss with family prior to making a decision.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) or study site.

- Participants will be encouraged to ask any questions at any time for any reason, and to seek outside counsel when appropriate.
- To verify informed consent was obtained before the participant was enrolled in the study, the ICFs will contain the date and time written consent was obtained. The authorized person obtaining informed consent must also sign the ICFs.
- Participants must be re-consented to the most current version of the ICFs during their participation in the study, per institutional IRB requirements, and they will be informed of any changes to the consent form.
- A copy of the ICFs must be provided to the participant.

The ICF and any other written participant information to be provided to participants will be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised ICF and written participant information will receive IRB approval before being implemented. The participant will be informed of any changes and re-consented with the current version of the consent form and provided a copy at their next visit. Communication of this information to the participant will be documented.

The informed consent process may be handled remotely, see the MoP for full details.

5.3.1 Informed Consent Comprehension

The informed consent comprehension process will serve as a way to engage with potential research participants about their study participation. Prior to signing the ICF, the person facilitating the consent process will assess the participant's comprehension of the study, via an Informed Consent Form Process Checklist, and their understanding of what the study involves by asking specific study-related questions. The questions will serve as a way to identify areas where the participant may lack understanding. In that case, those sections of the consent will be reviewed again until comprehension is achieved.

5.4 Screening Visit (7-35 days)

After preliminary eligibility is determined via the Telephone Screen, the Screening visit will confirm eligibility for the study. Screening will occur in an appropriate venue at each study site, and certain assessments may be conducted remotely (see [Table 1](#) and the MoP for full details). Upon signing the Informed Consent Form (ICF), the potential participant may commence study-related screening activities. No study related procedures, other than the study pre-screening questionnaire and telephone screen, will occur prior to obtaining written informed consent.

Screening will take 7 to 35 days to allow for full medical and psychiatric evaluation and to allow for psychiatric medication taper ([Section 4.2.1](#)), if needed, prior to Baseline. It is expected that Screening may require multiple days/visits to reduce participant burden and allow for appropriate assessment. The purpose of the Screening visit is to evaluate medical and psychiatric appropriateness for the study. If at any point the participant is found to be ineligible, the screening process may be discontinued and any remaining procedures will not take place.

5.4.1 Medication Taper

As was reviewed in [Section 4.2.1](#), only participants who agree and have been successfully tapered off their psychiatric medications are eligible. Psychiatric medications will be tapered based on standard of care tapering for each medication per the direction of the study psychiatric medical provider. Guidelines will also be provided in the MoP, which study medical providers can utilize to guide the taper.

5.4.2 Suspending Outside Psychotherapy

As was covered in [Section 4.2.2](#), participants will only be eligible for study enrollment if they agree and are judged able to suspend any ongoing outside psychotherapy for the duration of study involvement. If deemed appropriate, communication between the outside psychotherapist and/or psychiatrist (if one had been previously established), the Lead Facilitator, and study clinicians at each site will be coordinated following informed consent. However, because clinical care for study participants will be assumed by study clinicians following enrollment, active discussions among an outside psychiatrist or psychotherapist and study clinicians will occur only in case of an emergency or psychiatric need until the study's final end-point (Day 43).

5.5 Baseline Visit (maximum 7 days prior to dose)

The Baseline visit will occur at the end of the screening process, following completion of all screening procedures, including medication tapering ([Section 5.4.1](#)). For the timing and frequency of assessments see [Table 1](#). This visit will occur in-clinic, though certain assessments may be conducted remotely (see [Table 1](#) and the MoP for full details).

5.5.1 Inclusion/ Exclusion Criteria Confirmation

Following the completion of all Screening and Baseline medical and psychiatric assessments, the PI will confirm participant eligibility on an ongoing basis until dosing.

5.6 Re-Screening

Participants may be eligible for re-screening at the discretion of the site PI or MD, including participants who screen fail or who are unable to complete the screening assessments within 35 days (including requirement for slow medication tapering due to withdrawal symptoms). The purpose of the re-screen is to assure continued safety and eligibility for participating in the study. Re-screening includes repeating all screening assessments. However, if a subject is found to be ineligible at any point during the re-screen process, the re-screen will be discontinued at that point. A participant who is rescreened is not required to sign another ICF unless a new version of the ICF has been approved since the date the original ICF was signed.

6 PREPARATION, RANDOMIZATION, DOSING AND FOLLOW UP PROCEDURES

This section outlines the purpose and content of all preparation, randomization, dosing and follow up study procedures. Participants will be provided with visit reminders. For the timing and frequency of assessments at each visit see [Table 1](#). Full details are provided in the MoP.

6.1 Preparatory Sessions with Clinical Facilitators (1-6 days prior to dose)

Following successful completion of Screening and Baseline, participants will be assigned a Lead Clinical Facilitator and a Co-Facilitator. Both Facilitators will remain with the participant throughout the preparatory and integration sessions to the greatest extent feasible. For the entirety of the dosing session both Facilitators will be present in the session room and will attend to the participant to continuously observe and evaluate the participant's physical and mental status, with the exception of infrequent, short and unavoidable breaks (e.g. facilitator bathroom breaks). Such breaks are expected to be minimal and kept to the shortest possible duration. At least one Facilitator will always be present in the session room with the participant. For criteria required to be a Session Facilitator see [Section 6.3.2](#).

The main objective during preparatory sessions is to build rapport and therapeutic alliance between the participant and Session Facilitators, which can support the participant as they navigate the dosing session. Participants will meet with one or both of the Facilitators who will attend the participant's study dosing session. Whenever possible, these meetings will occur in the room in which dosing will take place so participants can develop a level of comfort and familiarity with the intervention location. If necessary, the meetings may be held remotely; however, one in-person preparatory session should be conducted. Consistent with previous psilocybin protocols, the participant's life history and current situation in life will be reviewed, and intentions and expectations for the intervention session will be discussed. It is also expected that the participant's support person will meet the session Facilitators before dosing. For the specific contents and structure of the preparatory sessions see the Usona Facilitator Training Manual.

The pre-intervention preparatory sessions will occur as follows:

- approximately 6-8 hours of preparation, which can occur over multiple days in the 1-6 days prior to intervention

The reason for allowing for multiple days is to reduce participant burden due to the number of hours of preparation required to cover all content.

6.1.1 Post Preparatory Session Assessment (1-4 days prior to dose)

This assessment can occur on the same day as the last preparatory assessment but must be performed after all preparatory session activities are complete. These assessments may be conducted remotely (see [Table 1](#) and the MoP for full details). The assessment will include the 'Since Last Visit' C-SSRS as an additional safety check prior to administration of the study drug. Before dosing, Facilitators will communicate with the PI and Study Physician to discuss overall

appropriateness for dosing. If the Facilitators, PI or Study Physician believes the dosing session is contraindicated, the session will be cancelled or postponed.

6.2 Randomization

Randomization will occur following Screening, Baseline, and specific Day 1 (dosing day) assessments (i.e., vital signs, urine pregnancy test, urine drug test, and eligibility verification) for participants who have been determined to be eligible for the study. Randomization will occur on Day 1 (dosing day) prior to the participant being dosed. Prior to randomization, participants will be stratified by study site. Following this, participants will be randomized to one of two intervention groups in the EDC system. A centralized, computer-generated randomization schedule will be created in which participants are randomized in a 1:1 ratio in a blinded fashion to the psilocybin group or the active control group. Once data collection from the assessments required for participant randomization is complete and study eligibility is verified, the database will assign an intervention group code.

The master randomization code will be maintained in a secured location until the time of unblinding.

In the event of unforeseen circumstances that prohibit use of the database to generate the randomization assignment, procedures for determining the assignment manually are available and are described in the MoP.

6.3 Day 1: Dosing Session

Participants will be asked to report to the research site in the morning. Sessions are expected to last 7-10 hours, on average.

6.3.1 Pre-Dose

Upon arrival, and prior to the dosing, the following assessments will occur:

1. Study personnel will inquire about any possible changes in health
2. Study personnel will inquire about any change in concomitant medication use and adherence.
3. A urine drug test for drugs of abuse will be performed
4. Urine pregnancy testing (women of childbearing potential only) will be performed
5. The study coordinator will remind the participant of their agreement to the following during the dosing session, as previously agreed to during the preparation sessions (also see Manual for Clinical Facilitators for agreements):
 - The participant agrees to remain on-site for a minimum of 7 hours on their dosing day after ingesting the psilocybin or placebo capsule and all identified study personnel agree that the participant may safely leave the facility with their identified support person.
 - The participant agrees to not harm himself or herself or anyone else during the dosing day.

- The participant agrees to refrain from damaging any property during the dosing day.
 - The participant agrees to call the site and/or 911 if he or she has suicidal thoughts or feelings throughout the duration of the study.
6. Pre-Dose vital signs (Blood Pressure and Heart Rate)
 7. SMDDS will be completed by participant

Urine Drug Test Results

A negative urine drug test will be required the morning of dosing prior to drug administration. A positive urine drug test will result in the dosing session being canceled. The Study Physician will be notified of urine drug test results. A positive urine drug test will result in the dose being canceled with no option for future rescheduling.

Pregnancy Test Results

A negative urine pregnancy test (women of childbearing potential only) will also be required the morning of dosing prior to drug administration. The Study Physician will be notified of urine pregnancy test results. A positive pregnancy test will result in the dose being canceled with no option for future rescheduling.

Pre-Dose Cardiovascular Monitoring

Table 2: Pre-Dose Blood Pressure Monitoring

Cardiovascular Monitoring (Blood Pressure): Pre-Dose		
Blood pressure will be obtained prior to dose administration ¹ . Blood pressure assessments will be conducted by trained study personnel. The following safety parameters have been established:		
Result		Instructions
SBP < 140 mmHg and DBP < 90 mmHg	Acceptable	Proceed with dosing
SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	High	Wait a minimum of 5 minutes and repeat blood pressure to determine if elevation is temporary. Participant should continue to remain recumbent.
		If repeat BP is < 140 mmHg and < 90 mmHg, proceed with dosing
		If three readings are elevated ² , consult with the study physician for further evaluation and follow up. The dose will be canceled and rescheduled ² at the discretion of the site PI and study physician.

¹ The initial reading should occur after the participant has been recumbent a minimum of 10 minutes

² Dosing may be rescheduled at the discretion of the site PI or study physician. If > 7 days have elapsed since the Baseline visit, all Baseline measures must be repeated before dosing. If > 35 days have elapsed since the participant initially consented, the participant will require complete re-screening for study participation.

Table 3: Pre-Dose Heart Rate Monitoring

Cardiovascular Monitoring (Heart Rate): Pre-Dose		
Heart rate should be obtained prior to dose administration ¹ . Heart rate assessments will be conducted by trained study personnel. The following safety parameters have been established:		
Result		Instructions
≥ 50 BPM and ≤ 100 BPM	Acceptable	Proceed with dosing
< 50 BPM or >100 BPM	Low (<50 BPM)/ High (>100 BPM)	Wait a minimum of 5 minutes and heart rate to determine if decrease or elevation is temporary. Participant should continue to remain recumbent.
		If repeat HR is ≤ 100 BPM and ≥ 50 BPM proceed with dosing
		If three readings are decreased or elevated, consult with the study physician for further evaluation and follow up. The dose will be canceled and rescheduled ² at the discretion of the site PI and study physician.

¹ The initial reading should occur after the participant has been recumbent a minimum of 10 minutes

² Dosing may be rescheduled at the discretion of the site PI or study physician. If > 7 days have elapsed since the Baseline visit, all Baseline measures must be repeated before dosing. If > 35 days have elapsed since the participant initially consented, the participant will require complete re-screening for study participation.

6.3.2 Dosing

Following successful completion and acceptable results of the above scheduled assessments the participant will be dosed. When the participant is ready he or she will receive a single dose of the study drug (25 mg psilocybin or 100 mg niacin placebo), administered as a capsule and taken with approximately 8 ounces of water. Regardless of the study drug received, the participant will be under observation for at least 7 hours following ingestion.

Following study drug ingestion, it is recommended that study staff entering the session room be limited to the two Facilitators, the Study Physician, and the person obtaining vital signs (if not the Facilitator). Only in the event of an emergency should additional study staff enter the room, including the Study Coordinator, PI, and Co-I (if not the Facilitator). The rationale for minimizing who enters the session room is to reduce distractions for the participant.

Session Facilitators

Lead Facilitators at all study sites will be doctoral level psychotherapists with experience in the psychological treatment of MDD. Specifically, the Lead Facilitators will be Clinical and Counseling Psychologists (PhD/PsyD) or psychiatrists and appropriately trained/experienced physicians (MD or DO). Co-Facilitators at all study sites will hold a minimum of a bachelor's degree in a mental health field. Both Lead and Co-Facilitators will have adequate training to identify safety issues during the participant's preparation, dosing, and integration sessions, and will have undergone specific Usona Clinical Facilitator training. See the Usona Clinical Facilitator Manual for details.

For the entirety of the dosing session both Facilitators will be present in the session room and will attend to the participant to continuously observe and evaluate the participant's physical and

mental status, with the exception of infrequent, short and unavoidable breaks (e.g. facilitator bathroom breaks). Such breaks are expected to be minimal and kept to the shortest possible duration. At least one Facilitator will always be present in the session room with the participant. Continuous supervision provides a safety structure and ensures that the participant will receive reassurance and emotional support from the Facilitators should he/she experience strong emotions or become anxious or agitated during the session. Specific dosing session safety monitoring, via the Facilitator Monitoring Form, will be conducted at regular, pre-specified times through assessment of the following: nausea, acute physical or psychological distress, including self-harm, and self-reported anxiety. This is intended to provide Facilitators with an enhanced ability to monitor participant safety and communicate any observed symptoms to the Study Physician, who will determine if immediate clinical assessment is warranted.

Role of the Study Physician During Dosing

The on-call Study Physician is responsible for the overall safety of participants, and he/she will oversee the medical management of study participants during the dosing session, as needed.

- Availability during Dosing: The Study Physician will be on-call throughout the duration of the dosing session and will need to be available to be onsite within approximately 5 minutes in the event of an emergency for medical/psychiatric assessment. The Study Physician is responsible for administering rescue medications, should these be warranted.
- End of Dosing Day: The Study Physician will assess the participant in-person at the end of the dosing day to determine if he/she is ready to be released from the research site.
- Overnight: The Study Physician will be on-call following participant release and until the following morning when the participant returns for his/her integration session.

Rescue Medications Available During Dosing

In the unlikely event that a participant requires medication management for blood pressure, anxiety or psychosis, the study physician may use the following medications (or similar medications available on site) per his/her medical discretion:

1. Nitroglycerin
2. Clonidine
3. Diazepam
4. Risperidone

The use of rescue medications to control symptoms will be at the judgment of the treating physician, therefore use of specific medications is not protocolized. The study site will supply the rescue medications, which will be obtained locally at each institution. The date and time of medication administration, reason for administration, as well as the name and dosage regimen of the rescue medication must be recorded on the Concomitant Medications log. Use of psychotropic agents (e.g. diazepam, risperidone) will be on a single dose/time limited basis and hence will not fall under the study exclusionary criteria regarding chronic use of these agents prior to enrollment.

In the unlikely event of a medical or psychiatric emergency that cannot be safely managed by staff with reassurance or pharmacological intervention, the study physician will determine if the participant can be safely escorted by medical staff to the nearest emergency department, or if 911 needs to be called for transport.

Cardiovascular Monitoring During Dosing Session

Blood pressure and heart rate will be obtained at 30, 60, 90, 120 minutes, 4, 6, and 7 hours after drug administration. Participants will not be discharged until after the 7-hour blood pressure and heart rate assessments have been completed. Measurements must be collected within +/-10 minutes of the scheduled time point. Measurements will be conducted by trained study personnel. Blood pressure measurements should occur after the participant has been recumbent a minimum of 10 minutes.

Table 4: Blood Pressure Monitoring during Dosing

Cardiovascular Monitoring (Blood Pressure): Dosing Session	
The following Blood Pressure safety parameters have been established for the dosing session:	
Result	Instructions
SBP \leq 170 mmHg and DBP \leq 95 mmHg	No additional follow up needed, take BP at next scheduled time point.
SBP $>$ 170 and $<$ 200 mmHg or DBP $>$ 95 and $<$ 110 mmHg	Repeat every 5 minutes for a total of three readings over 15 minutes. <ul style="list-style-type: none"> • If three or more readings are elevated consult with the study physician
SBP \geq 200 mmHg or DBP \geq 110 mmHg	Consult with the study physician for further evaluation and follow up. Medication and medication administration is at the clinical judgment of the Study Physician and is not protocolized. The following medication administration is a recommendation; however, the Study Physician may treat the participant based on his or her own judgement and with the medications ¹ available on site. <ul style="list-style-type: none"> • The participant may be treated with sublingual nitroglycerin¹ 0.4 mg • If blood pressure readings do not decrease below these thresholds after 5 minutes, the same dose of nitroglycerin will be administered • A third dose of nitroglycerin¹ will be given after another 5 minutes, if readings remain elevated above these levels (maximum dose is 0.4 mg x 3) • If blood pressure remains \geq200 systolic or \geq110 diastolic, at the judgment of the study physician, the participant will be treated with oral clonidine¹ (e.g., 0.1 mg) and the Study Physician will evaluate whether transport to the emergency room is necessary.

¹ Administration of any medications must be recorded on the Concomitant Medications form

Table 5: Heart Rate Monitoring during Dosing

Cardiovascular Monitoring (Heart Rate): Dosing Session	
The following Heart Rate safety parameters have been established for the dosing session:	
Result	Instructions
$<$ 50 BPM	Repeat every 5 minutes for a total of 3 readings over 15 minutes. <ul style="list-style-type: none"> • If three or more readings are below 50 BPM consult with the study physician
\geq 50 BPM and \leq 110 BPM	No additional follow up needed, take HR at next scheduled time point.
$>$ 110 BPM	Repeat every 5 minutes for a total of three readings over 15 minutes <ul style="list-style-type: none"> • If three or more readings are elevated consult with the study physician

The final scheduled vital signs assessment is at 7-hours post-dosing, with the following safety parameters/ instructions.

Table 6: 7-hour Blood Pressure and Heart Rate Monitoring

Cardiovascular Monitoring: 7-hour Measurement		
The following safety parameters have been established for the End of Dosing Day (7-hour) blood pressure (BP) and heart rate (HR) measurements ¹ .		
BP Result	HR Result	Instructions
SBP < 140 mmHg and DBP < 90 mmHg	< 100 BPM	No action needed. The participant may be released.
SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	≥ 100 BPM	Participant should continue to remain recumbent. Wait a minimum of five minutes and repeat measurement to determine if elevation is temporary. The measurement can be repeated up to three times, separated by a minimum of five minutes, with the participant remaining recumbent. Document any additional measurements.
SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	≥ 100 BPM	<p>If there are three consecutive readings of SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, contact the Study Physician for further in-person evaluation and follow-up.</p> <ul style="list-style-type: none"> • The participant may be released if the Study Physician does not feel the elevated measurement is concerning. • If the Study Physician feels the elevation is concerning, the participant will remain on site for further evaluation. If the Study Physician feels medication administration² is warranted, he/she can treat the participant with medications available at the site. • If the participant responds to either waiting or medication administration, and the measurement decreases to a level the Study Physician does not feel is concerning, the participant may be released. • If the participant does not respond and the Study Physician feels the elevation is concerning and warrants further evaluation, Study Physician will evaluate whether transport to the emergency room is necessary.

¹ Heart rate and blood pressure measurements should occur after the participant has been recumbent a minimum of 10 minutes

² Administration of any medications must be recorded on the Concomitant Medications form

6.3.3 Post-Dosing Release Procedures

Following the 7-hour vital sign assessment, if the participant appears to have returned to his/her baseline psychological and physiological state and expresses a readiness to begin the discharge process, the Lead Facilitator and Study Physician will assess the participant using the Participant Release Form (for a copy of the form see the Manual of Procedures). This assessment will confirm whether the participant is ready to safely leave the research facility accompanied by his/her support person (family or a trusted friend). This support person will have already been identified and briefed by Facilitators on basic guidelines for accompanying the participant home during preparation session #2. Self-care activities and additional safety precautions will be reviewed with the participant before the participant and support person leave the premises.

If the participant is experiencing residual study drug effects, such as mild persistent sensorial distortions, he or she will be asked to remain on-site for continued observation by Facilitators and/or the attending physician until cleared to leave with the support person.

While it is unlikely, if it is found that the participant is experiencing severe persisting physical or perceptual drug effects or is exhibiting signs of significant/severe emotional distress including suicidal ideation, or any other circumstance deemed an emergency per the Study Physician, the Study Physician will evaluate the participant for transport to the emergency department by study personnel for further assessment.

The participant will be given a post-dosing session summary form which they can use to record recollection of the dosing session before returning for Integration Session #1 on Day 2. This summary may be reviewed with the participant throughout the integration sessions. Additional details about this summary can be found in the Manual for Clinical Facilitators.

The Lead Clinical Facilitator, Co-Facilitator, and Study Physician will be on-call throughout the night to speak with the participant or support person should any issues or safety concerns arise.

6.4 Day 2: Post Dose

The Day 2 visit will occur in person, though certain assessments may be conducted remotely (see [Table 1](#) and the MoP for full details). The purpose of the Day 2 visit is to assess the participant for safety and to allow for integration of the dosing session with the session Facilitators.

6.5 Day 5: Post Dose Phone Call (±1 day)

Five days post-dose, study personnel will contact participants by phone. The primary goal of this telephone contact will be to ensure participant safety. Each call will last on average 5-15 minutes but could be longer to address participant concerns and to adequately assess wellbeing. In consultation with the site PI, additional telephone contact can be initiated at the request of study personnel, Facilitators or the participant.

6.6 Day 8, 15 and 29: Post Dose (-1/+2 days)

Day 8 consists of collection of the primary study outcome as well as other safety and efficacy outcomes, and Days 15 and 29 allow for continued safety and efficacy follow-up. These visits will occur in person, though certain assessments may be conducted remotely (see [Table 1](#) and the MoP for full details).

6.7 Day 9 and 16: Integration Sessions #2 and #3 (-1/+4 days)

The purpose of these visits is to allow for further integration of the dosing session. These visits take place in person unless specific circumstances do not allow the participant to attend in person. In that case, video conferencing or phone calls will be arranged.

Day 9 and Day 16 visits can occur on Days 8 and 15, respectively, and must take place after all Day 8 and Day 15 procedures and assessments have taken place.

6.8 Day 43: Post Dose/End of Study (± 3 days)

This visit will occur in person, though certain assessments may be conducted remotely (see [Table 1](#) and the MoP for full details). These assessments will constitute study termination measures. After all study measures and assessments are completed, the participant is considered to have completed the study. The study team will also discuss the End of Study plan, described below.

Whenever possible, participants who have withdrawn from the study but agree to follow-up will also complete this assessment.

6.8.1 End of Study Plan

During Integration Session #3, Facilitators will discuss the participant's plans after the study has ended. The study clinician and/or PI will confirm the End of Study plan at the Day 43/ End of Study visit. Additionally, study participants will be referred back to their primary care provider, psychiatrist or therapist for additional follow up as needed. Any verbal or written handoff will be documented.

6.9 Blinding Related to Delivery of Study Interventions and Collection of Outcome Data

As with any interventions that produce noticeable psychological effects following administration, blinding psilocybin poses unique challenges. Several strategies will be employed to minimize the impact of the blinding challenges posed by psilocybin. Most importantly, the study's primary outcome assessment (MADRS) will be conducted by remote blinded central raters who will have no interactions with either participants or study personnel other than conducting the MADRS assessments, which will be conducted by telephone, as is standard practice when central raters are used in pharmaceutical trials. These raters will have no information regarding specifics of the study design and will not know where in the study protocol any given participant is when assessed.

Prior to site activation, all study site staff will receive extensive training in basic research principles of maintaining the study blind and ensuring only appropriate personnel have access to this information. Blinding will be consistent at each site through the use of study specific procedures defined in the MoP.

Session Facilitators, who will be in the room with participants throughout their dosing sessions, may become functionally unblinded as a result of participants demonstrating changes in behavior and/or speech suggestive of a psychedelic experience, or as a result of participants not demonstrating these types of changes. To reduce the risk that these potentially unblinded Facilitators might unintentionally unblind personnel who will assess symptom status via central rater interviews with the participants after the dosing sessions, Facilitators will have no contact with the remote central raters who will assess the primary study outcome.

6.9.1 Unblinding Procedure

Full blinding of study personnel, the Sponsor and participants will be maintained until data lock at the conclusion of the study. Exceptions on an individual subject basis will be made in cases in which it is determined by site PI, the Medical Monitor or the Sponsor that unblinding of a participant's intervention assignment is required for participant safety. Anyone requesting individual unblinding prior to study-wide unblinding will first be referred to the site PI. The site PI must notify the medical monitor of the request and discuss the circumstances surrounding the request. The medical monitor will notify the Study Coordinating (SCC) Project Director, the study director and the Sponsor's medical expert of the request and if unblinding occurred. Attempts should be made to maintain the blind of the investigators prior to the study-wide unblinding. Unblinding during the study will be recorded on the Protocol Deviation Form. All instances of unblinding must be reported to the site IRB, the Sponsor's medical expert, and the study director. The details of the process for maintaining the blind and for unblinding are described in the MoP.

6.10 Early Termination Visit

Should a participant terminate early, including Prep Phase Terminations and participants who are randomized and later terminate or are terminated for safety reasons (see [Section 7.3.3](#)), the End of Study visit assessments will be completed to the extent possible within 14 days. The End of Study Plan will be discussed at the termination/End of Study visit. An End of Study visit will not be conducted for Screen Failures (for more information on Screen Failures see [Section 7.1](#)).

6.11 Unscheduled Visits

Unscheduled visits are any visits conducted to perform additional procedures other than regularly scheduled visit procedures, including additional integration sessions, if needed. Procedures performed will be based on the clinical judgment of the PI, Study Physician, or session Facilitators. Procedures and results will be recorded as an Unscheduled Visit.

7 STUDY DISCONTINUATION AND COMPLETION CRITERIA

7.1 Screen Failures

Screen Failures are defined as participants who are deemed ineligible either at the Screening or Baseline assessment. Screen failures may fail to meet one or more Inclusion Criteria and/or may meet one or more Exclusion Criteria or withdraw consent. Screen Failures may be identified by various ways, including review of medical history, assessments, measures, laboratory results, or conversations with the participant. Medical assessments may be repeated for confirmation. At any time during Screening, if a potential participant is deemed to be ineligible and therefore qualify as a Screen Failure, study personnel will notify the potential participant that he/she is not eligible and no additional Screening assessments will be scheduled or conducted. All potential participants who begin Screening will be tracked in the EDC study database and reasons for Screen Failure will be recorded.

At the discretion of the site PI or Study Physician, participants who screen fail may be eligible to be re-screened. See [Section 5.6](#) for Re-Screening requirements.

Screen Failures may request or be referred to an outside mental health clinician/ medical provider or to their health care provider, if needed.

Screen Failures are not considered evaluable.

7.2 Evaluable Participants

A participant is considered evaluable and eligible for the ITT analysis if he or she meets study eligibility criteria and is randomized to psilocybin or active placebo.

7.3 Early Termination from the Study

Participants can withdraw consent or terminate from the study at any time at his/her request without prejudice. Study personnel can withdraw a participant if, in their clinical judgment, it is in the best interest of the participant or if the participant cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If study personnel withdraw a participant from the study, study personnel will explain the reason for withdrawing the participant. The reason for early termination will be recorded.

Randomized participants who prematurely terminate from the study will not be replaced.

7.3.1 Early Termination Post-Baseline and Pre-Randomization (Preparation Phase Termination)

It is possible that participants will discontinue study participation between the end of the Baseline assessments and up to randomization on the morning of dosing. This might occur for any of following reasons, including, but not limited to, a decision to withdraw, a decision on the part of site personnel to withdraw the participant prior to dosing, a change in mental or physical health status, or become ineligible to be randomized during the preparatory sessions. These participants will be considered Preparation Phase Terminations and will complete an End of

Study visit (see [Section 6.9](#)) within 14 days. Similar to Screen Failures, these participants will not be included in the ITT analysis population but will be included in the safety analysis population.

7.3.2 Early Terminations Post-Randomization and Pre-Dosing

If a participant is terminated or withdraws post-randomization but prior to dosing, he/she will be encouraged to continue with all scheduled follow-up assessments if it is safe to do so. Data from these participants will be included in the ITT analysis population as well as the safety analysis population.

7.3.3 Early Termination Post Dosing

If a participant develops any condition post-dosing that, in the opinion of the PI (and upon consultation with the study Sponsor as needed), would negatively impact safety should he/she remain in the study, the participant will be asked to complete the End of Study visit within 14 days. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI, Medical Monitor and/or Sponsor.

For other post-dosing exclusion criteria not judged to impact participant safety, participants will be encouraged to remain in the study and continue with all follow up assessments, given that no additional exposure to the study medication is required following the dosing day. If a participant does not agree to remain in the study, or if a participant chooses to withdraw from the study for any other reason post-dosing, he/she will be asked to complete the End of Study visit assessments within 43 days of their dosing day, so that the maximal time between dosing and assessment is no longer than the time period for participants who complete the study.

7.3.4 Dropouts

If a participant withdraws consent they will be terminated from the study without further follow up. These participants are defined as dropouts. If they withdraw consent prior to or during Baseline they are considered Screen Failures. If they withdraw consent post dosing then study records/data generated until the date consent is withdrawn will remain available for use by the Sponsor and PI.

7.3.5 Lost to Follow-up Post Dosing

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits post dosing and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the PI or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if

necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.3.6 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Assessments.

7.3.7 Premature Study Discontinuation

The Sponsor, FDA, IRBs, and Data Monitoring Committee have the right to discontinue this study at any time. If the trial is prematurely terminated, the PI is to promptly inform the study participants and will assure appropriate referral and follow-up. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the Sponsor and will be treated in accordance with federal and state regulations.

8 INVESTIGATIONAL PRODUCT

8.1 Description of Investigational Product

The investigational product (IP) to be used in this protocol is psilocybin, a tryptamine that produces its behavioral effects primarily by acting as post-synaptic agonists at serotonin 5-HT_{2A} and 5-HT_{2C} receptors (Sanders-Bush & Mayer, 2006). Refer to the IB for a comprehensive review of the pharmacology, effects and proposed mechanisms of action of psilocybin.

8.2 Description of Active Placebo

Niacin, also known as nicotinic acid or vitamin B3, will be used as the active placebo in this protocol. Upon ingesting niacin, one commonly experiences a physiological reaction including warmth or flushing of the skin and mild dizziness.

8.3 Source

Usona Institute has contracted the manufacture of cGMP psilocybin (active pharmaceutical ingredient), cGMP psilocybin capsules (25 mg) and cGMP niacin capsules (100 mg). Compendial grade (USP) niacin will be used in the preparation of the niacin active-control drug product.

8.4 Study Drugs Administered

Identical capsules will contain either 25 mg of psilocybin or 100 mg of niacin. Each capsule is provided in an HDPE bottle; bottles of study medication will be stored in the research pharmacy or other DEA-approved storage location of each study site. A capsule will be provided to a participant at the appropriate time during the dosing session. The participant will swallow the capsule with water.

Table 7: IP and Active Placebo Information

Study Intervention Name:	Psilocybin Capsule (active drug product)	Niacin Capsule (active placebo product)
Dosage formulation:	One active capsule contains 25 mg of psilocybin	One active placebo capsule contains 100 mg of niacin
Capsule:	Size 2 HPMC, white opaque	Size 2 HPMC, white opaque
Unit dose strength:	25 mg25 mg25 mg25 mg	100 mg100 mg100 mg100 mg
Route of Administration:	Oral (solid dose)	Oral (solid dose)
Dosing instructions:	One capsule administered with water	One capsule administered with water
Packaging and Labeling:	Study Intervention will be provided in an HDPE bottle. Each bottle will contain one capsule (psilocybin or niacin) and will be labeled as required per country requirement for blinded study.	

8.5 Dosing

Participants in this study will receive one dose of either psilocybin or niacin during their dosing session. Participants randomized to psilocybin will receive a 25 mg of psilocybin taken with approximately 8 ounces of water. Participants randomized to niacin will receive 100 mg of niacin taken with approximately 8 ounces of water.

8.6 Drug Delivery, Storage, Handling, and Accountability

1. The PI or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study medication.
2. Only participants randomized in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the PI and authorized site staff.
3. The PI (or designee) is responsible for study medication accountability, reconciliation, and record maintenance (receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study medications are provided in the Pharmacy Manual.

9 STATISTICAL CONSIDERATIONS

Full details of statistical analysis will be provided in the statistical analysis plan (SAP).

9.1 Hypotheses

Primary Study Objective: To evaluate the impact of a single administration of psilocybin on depressive symptoms in patients with MDD when compared to an active niacin placebo

Hypothesis 1.1 (PRIMARY STUDY HYPOTHESIS): When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in central rater MADRS scores from Baseline to Day 43 post intervention (primary study outcome).

Hypothesis 1.2: (KEY SECONDARY STUDY HYPOTHESIS) When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in central rater MADRS scores from Baseline to Day 8 post-dose (key secondary study outcome).

Hypothesis 1.3: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in significantly higher rates of sustained response, defined as a $\geq 50\%$ reduction from Baseline central rater MADRS scores to Day 8, 15, 29 and 43 post-dose (secondary study outcome).

Hypothesis 1.4: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in significantly higher rates of sustained remission, defined as a central rater MADRS scores ≤ 10 from Baseline to Day 8, 15, 29 and 43 post-dose (secondary study outcome).

Hypothesis 1.5: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in central rater MADRS scores from Baseline to Day 2, Day 15 and 29 post-dose (exploratory study outcome).

Hypothesis 1.6: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in SMDDS scores from Baseline to Day 8 and 43 post-dose (exploratory study outcome).

Hypothesis 1.7: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in SMDDS scores from Day 1 (pre-dose) to Day 8 and 43 post-dose (exploratory study outcome).

Hypothesis 1.8: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in ODQ scores from Baseline to Day 43 post-dose (exploratory study outcome).

Specific Aim 2: To evaluate the impact of a single administration of psilocybin on functional disability in patients with MDD when compared to an active niacin placebo

Hypothesis 2.1: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in SDS scores from Baseline to Day 43 post-intervention (secondary study outcome).

Hypothesis 2.2: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in SDS scores from Baseline to Day 8, 15, and 29 post-dose (exploratory study outcome).

Specific Aim 3: To evaluate the impact of a single administration of psilocybin on anxiety symptoms in patients with MDD when compared to an active niacin placebo

Hypothesis 3.1: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant reduction in HAM-A scores from Baseline to Day 8, 15, 29 and 43 post-dose (exploratory study outcome).

Specific Aim 4: To evaluate the impact of a single administration of psilocybin on quality of life in patients with MDD when compared to an active niacin placebo

Hypothesis 4.1: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant increase in the Q-LES-Q scores from Baseline to Day 8, 15, 29 and 43 post-dose (exploratory study outcome).

Hypothesis 4.2: When compared to a single administration of niacin placebo, a single administration of psilocybin will result in a significant decrease in CGI-S scores from Baseline to Day 8, 15, 29 and 43 post-dose (exploratory study outcome).

Specific Aim 5: To examine whether the occurrence of mystical-type or emotional breakthrough-type experiences in response to study medications predicts subsequent antidepressant responses

Hypothesis 5.1: Scores on MEQ-30 will be significantly higher post-dose in participants receiving a single administration of psilocybin than in those receiving niacin placebo (exploratory study outcome).

Hypothesis 5.2: Scores on the EBI will be significantly higher post-dose in participants receiving a single administration of psilocybin than in those receiving niacin placebo (exploratory study outcome).

Hypothesis 5.3: A significant indirect effect through post-dose MEQ-30 scores of the effect of treatment assignment, psilocybin compared to niacin, on change in central rater MADRS scores will be observed for the post-dose time point at which MADRS score differences between the psilocybin and niacin placebo groups are maximal (exploratory study outcome).

Hypothesis 5.4: A significant indirect effect through post-dose EBI scores of the effect of treatment assignment, psilocybin compared to niacin, on change in central rater MADRS scores will be observed for the post-dose time point at which MADRS score differences between the psilocybin and niacin placebo groups are maximal. (exploratory study outcome).

Specific Aim 6: To examine the relationship between central-rated and computer-administered MADRS measures of depressive symptoms

Hypothesis 6.1: Good agreement will be observed when comparing central-rated and computer-administered versions of MADRS scores at all time points (exploratory study outcome).

9.2 Power and Sample Size Determination

This Phase 2 study has been powered to evaluate the clinical efficacy of psilocybin for the primary and key secondary objectives, i.e. to test the difference between psilocybin and niacin in the change in central rater MADRS score from Baseline to Day 43 and Day 8 respectively, in the ITT analysis set.

Approximately 100 patients are planned to be randomized into this study. [Section 9.2.1](#) provides rationale for assumptions used in sample size calculations and [section 9.2.2](#) provides specifications of sample size calculations.

9.2.1 Rationale for Sample Size Assumptions

[Table 8](#) presents a review of studies of psilocybin in MDD, TRD and cancer-related anxiety and/or depression; additional details of these studies are described in the [Investigator's Brochure](#). In addition, data currently under embargo support a psilocybin-niacin difference on the MADRS of 8 points and a standard deviation between 9-10 points.

Because previous studies of psilocybin for depression have been designed as open label, cross-over, or wait-list control, and some studies have included multiple dosing sessions, effect size estimates from these studies should be utilized with caution in informing sample size assumptions for this randomized, double-blind, placebo-controlled trial. Two open-label studies of psilocybin in MDD (Davis et al., 2020) and TRD (Carhart-Harris et al., 2016) indicated 62% to 69% mean reduction in depression symptoms 1-week following the final dosing session in the psilocybin arms, and this reduction was sustained at 4-5 weeks post dosing with reduction in depression symptoms of 57% to 66% ([Table 8](#)). The two prior studies of psilocybin in cancer-related depression and anxiety showed a similar trend with a mean reduction in depressive symptoms at 5 weeks post dose of 71% in the high-dose group in Griffiths et al., 2016, and 57% reduction at 6 weeks post dose in Ross et al., 2016.

Based on changes over time observed in very low dose psilocybin, niacin, and delayed treatment groups of the previous studies, a decrease in depression symptoms from baseline to 43 days post-dose of approximately 30% in the niacin active-control arm is expected.

In the Carhart-Harris et al., 2016 study, a standard deviation for 1-week change from baseline in MADRS score was 9.9. Other studies of esketamine for MDD have reported MADRS change from baseline standard deviations of 12.0 to 14.0 ([FDA Ref ID 4392083](#)).

Dropout rates for time points around 6 weeks in prior studies were between 9-11% with the exception of the 0% dropout in the open label trial.

Table 8. Summary of Relevant Results from Prior Psilocybin Studies in Depression

Study	Indication	Study Design	Dosing Schedule	n ^a	Psilocybin Doses	Relevant Endpoint ^b /Timepoint	Treatment Arm	Baseline Mean (SD)	Post-Dose Mean (SD)	Change from Baseline Mean (SD) ^c	% Change from Baseline Mean (SD) ^c
Griffiths et al., 2016	Cancer-related anxiety and/or depression	Randomized, cross-over	Two Sessions	25	1 or 3 mg/70 kg (very low dose)	GRID-HAM-D/5 weeks	Very low dose psilocybin first	22.3 (4.4) ^d	14.8 (7.3) ^d	-7.5	-33.7
				26	22 or 30 mg/70 kg (high dose)		High dose psilocybin first	22.8 (4.9) ^d	6.6 (5.3) ^d	-16.2	-70.9
Ross et al., 2016	Cancer-related anxiety and depression	Randomized, niacin-controlled cross-over	Single Session	14	Single Session: 21 mg/70 kg	HADS Depression/1 week HADS Depression/6 weeks	Psilocybin first	5.29 (3.35)	2.00 (3.37)	-3.3	-62.2
							Psilocybin first		2.29 (3.37)	-3.0	-56.7
Carhart-Harris et al., 2016	TRD	Open-label	Two Sessions – 1 week apart	12	Session 1: 10 mg/70 kg (low dose), Session 2: 25 mg/70 kg (high dose)	MADRS/1 week	Single psilocybin arm	31.0 (5.0)	9.7 (9.9)	-21.3 (9.9)	-68.7 (33.2)
						QIDS/1 week	Single psilocybin arm	19.2 (2.0)	7.4 (4.9)	-11.8 (4.6)	-61.7 (23.9)
						QIDS/5 weeks	Single psilocybin arm		8.2 (5.4)	-11.0 (5.7)	-56.9 (29.3)
Davis et al., 2020	MDD	Randomized, wait list-control	Two Sessions – 1.6 weeks apart	13	Session 1: 20 mg/70 kg (moderately high dose), Session 2: 30 mg/70 kg (high dose)	QIDS/1 week	Immediate psilocybin arm	16.2 (3.6)	5.2 (4.6)	-11.0	-67.9
						QIDS/4 weeks	Immediate psilocybin arm		5.5 (3.6)	-10.7	-66.0
						GRID-HAM-D/1 week	Immediate psilocybin arm	22.9 (3.6)	8.0 (7.1)	-14.9	-65.1
						GRID/HAM-D/4 weeks	Immediate psilocybin arm		8.5 (5.7)	-14.4	-62.9

a. n = number of subjects receiving study product and completing follow-up assessments.

b. GRID-HAM-D = GRID Hamilton Depression Rating Scale; HADS = Hospital Anxiety and Depression Scale; QIDS = Quick Inventory of Depressive Symptomatology.

c. Means estimated from baseline and post-dose means presented in publication for Griffiths et al., 2016, Ross et al., 2016, Carhart-Harris et al., 2016, and Davis et al., 2020. Means and standard deviations calculated from raw data for Carhart-Harris et al., 2016.

d. SD calculated from Standard Error of Mean presented in publication.

9.2.2 Sample Size Calculations

Simulations were generated to estimate power for a primary endpoint of MADRS change from baseline to Day 43 and key secondary endpoint of MADRS change from baseline to Day 8 assuming a MMRM model as specified in [Section 9.4.1](#).

Assuming a placebo group MADRS mean change from baseline = 10 at all time points, MADRS change from baseline SD = 10, psilocybin group MADRS mean change from baseline at Day 8 = 18 ($d = 0.8$) and Day 43 = 17 ($d = 0.7$), and 12.5% overall dropout by Day 43, a sample size of 100 participants would result in 92% power for primary Day 43 endpoint and 98% power for the key secondary Day 8 endpoint. Additional details regarding sample size calculations are provided in the PSIL201 Statistical Analysis Plan.

Key assumptions are in alignment with what has been observed in previous psilocybin studies noted in [Section 9.2.1](#).

9.3 Populations for Analyses

Efficacy analyses of primary, secondary and exploratory outcomes will be conducted on an ITT population that will include all randomized participants. Participants who withdraw from the study for any reason after receiving a study intervention but prior to the Day 43 assessment will be asked to complete an exit assessment of the primary study endpoint (change in MADRS score from Baseline to Day 43 post-dose).

Safety sets

The following populations will be used for analysis of safety data:

- **All Enrolled Population:** All participants who have signed written informed consent.
- **Safety Population:** Participants who were randomized and received study product.
- **Preparation Phase Termination Population:** Participants who discontinue study participation between the end of the Baseline assessments and up to randomization.

ITT set

Participants randomized to receive a study intervention (psilocybin vs. active placebo)

Per Protocol Set

Subset of the ITT set who received investigational product, completed post-dose Day 8 and Day 43 central-rater MADRS assessment, and have no major protocol deviations that may affect the primary or key secondary outcome measures.

9.4 Statistical Analyses

Descriptive statistics (proportions, means, standard deviation, quartiles) will be used to characterize Baseline demographic characteristics and continuous measures of behavioral response over time. Distributional features of all measurements will be evaluated, and data transformation (e.g., logarithm, rank transform) will be performed where indicated. Unless otherwise specified, all tests will be two-tailed with an alpha level set at $p < 0.05$.

9.4.1 Efficacy Analyses

The primary efficacy analysis will use a *de facto* estimand defined in alignment with the treatment policy strategy specified in [ICH E9 \(R1\)](#):

- **Treatment:** Psilocybin vs. niacin
- **Population:** All randomized subjects (ITT population)
- **Variable:** Change in central rater MADRS scores from Baseline to post-dose Day 43
- **Population-level summary:** Between-group difference in least squares means using MMRM model.

In the final ITT analysis, mixed effect models for repeated measures (MMRM) with an unstructured covariance matrix, with Baseline questionnaire score as a covariate and site, sex, and TRD status as fixed effects will be employed to test primary, key secondary, and other continuous secondary and exploratory study endpoints. Because Baseline score is included as a covariate, the primary outcome of interest will be between-group differences, however a treatment by time effect will also be included in MMRM to evaluate between group differences in the slopes of mean scores. For the primary, key secondary, and other continuous secondary and exploratory endpoints, MMRM will test whether there is a significant group difference at post-dose time points (i.e. Day 8, 15, 29 and 43). Hypothesis 1.1 (primary endpoint), Hypothesis 1.2 (key secondary endpoint), Hypotheses 1.3 and 2.1 (secondary endpoint) will be tested by a priori contrasts within the MMRM analysis regardless of whether the overall model is statistically significant. Exploratory hypotheses 1.5; 1.6; 1.7; 1.8; 2.2; 3.1; 4.1; and 4.2 will be evaluated similarly. For MMRM analyses, alternative covariance structures will be examined if an unstructured covariance matrix is found not to fit the data distribution.

Chi-square or Fisher's exact tests will be employed to test for between group differences in central rater MADRS-defined sustained response and remission (secondary endpoint, Hypotheses 1.3 and 1.4).

Hypothesis 6.1 will be evaluated using a measure of agreement such as intraclass correlation.

Alpha level for testing all endpoints will be $\alpha = 0.05$. To mitigate the risk of alpha inflation, a sequential significance testing procedure will be employed, such that testing of primary, key secondary, and other secondary hypotheses will proceed in the following pre-specified order with testing being halted upon the first confirmation of the null hypothesis (Hypothesis 1.1; 1.2;

2.1; 1.3; 1.4). Hypotheses associated with exploratory study endpoints will be tested with no adjustment made to the alpha level given the pre-specified exploratory nature of these hypotheses.

9.4.2 Mechanism-Based Exploratory Analyses

To conduct an exploratory analysis of the impact of mystical-type and/or emotional breakthrough-type experiences during the dosing sessions on subsequent longer-term antidepressant responses (Specific Aim 5), MEQ-30 and EBI scores post-dose will be compared between intervention groups using a two-sample t-test, or a Wilcoxon rank-sum test if data are not normally distributed. As a further exploratory analysis, structural equation modeling (path analysis) will be used to provide estimates of the magnitude and significance of hypothesized causal connections between MEQ and EBI score post-dose and subsequent antidepressant response at the post-dose time point at which MADRS score differences between the psilocybin and niacin placebo groups are maximal. By representing two pre-specified causal hypotheses (5.3 and 5.4) within a single input path diagram, the relative sizes of path coefficients in the output path diagram will indicate which behavioral construct (mystical-type vs. emotional breakthrough-type experience) explains more of the variance in psilocybin-induced antidepressant effects. Path analysis will also provide insight into potential causal relationships between emotional breakthrough and mystical-type experiences, should such relationships exist.

9.4.3 Safety Analyses

Qualitative safety analyses will examine safety data with summary tables listing concomitant medications/therapies, and AEs with frequencies and percentages tabulated overall, by group, and by Study Period. AEs will be tabulated by body system and coded for severity. Summaries of AEs, TEAEs, solicited AEs by severity will be provided. SAEs will be summarized similarly. AEs leading to discontinuation from the study will be listed and tabulated. Safety data collected for the period from Screening through the Baseline assessment and during the Preparation Phase will be presented separately from post-dose safety data. Laboratory values, physical examination finding and vital signs collected at study visits and vital signs collected during study dosing sessions will be summarized for all scheduled timepoints. Solicited AEs observed in randomized participants who received psilocybin with an incidence of 5% or greater and at least twice that of niacin placebo will be reported separately. AEs will be categorized according to Council for International Organizations of Medical Sciences (CIOMS) parameters, as follows:

- Very common: $\geq 1/10$
- Common (frequent): $\geq 1/100$ and $< 1/10$
- Uncommon (infrequent): $\geq 1/10000$ and $< 1/1000$
- Very rare: $< 1/10000$

When possible, statistical analyses will be used to evaluate selected safety outcomes by intervention group, as well as by relevant demographic characteristics (e.g., age, gender, ethnicity, severity of depressive symptomatology, and need for pre-intervention medication tapering).

9.4.4 Interim Analyses

No formal interim analyses are planned for this study. Accumulating data will be reviewed by the DSMB as specified in the PSIL201 DSMB Charter.

10 SAFETY MANAGEMENT

Below are the risks associated with participation in this study as well as the risk mitigation strategy associated with each risk. Safety measures will be applied, as described below, to minimize risks associated with participation in this study. This study proposes a combination of careful screening, preparation, supervision, and follow-up designed to minimize any risks.

Presented below are several domains that relate to adverse effects of psilocybin administration, which are further detailed in the IB. Following the section on psilocybin, the risks associated with the non-drug aspects of the study are described. Participation in this study may include risks that are currently unknown.

10.1 Risks Associated with Psilocybin

10.1.1 Physiological and Psychological Adverse Effects

The clinical safety of psilocybin has been extensively studied, both as a single agent and as adjunctive treatment in adult populations. Psilocybin is administered orally, and has been studied in open-label, and double-blind, controlled trials. Dosing regimens have ranged from 0.014 mg/kg to 0.6 mg/kg, administered as either a single dose, or multiple doses weeks apart.

Adverse event data from previous clinical trials has been used to evaluate the physiological profile of psilocybin. The IB for psilocybin summarizes the adverse event data collected from controlled clinical trials utilizing psilocybin in conjunction with cognitive enhancement therapy across multiple subpopulations.

The most likely potential acute adverse effects of psilocybin were shown to be anxiety, as well as panic, delusion, and cognitive impairments, particularly at higher doses (> 25 mg oral psilocybin) during the period of acute drug action. Such transient episodes of fear or anxiety respond well to reassurance and have not required pharmacological intervention. In previous clinical experience, acute psychological events were resolved by the end of the dosing day.

Overall, the most commonly reported physiological adverse events associated with psilocybin are:

- cardiovascular changes (including increased blood pressure and heart rate)
- nausea
- headache

These adverse events were generally classified as mild to moderate and were found to be transient in nature. No psilocybin-related serious adverse events were reported.

For this study, vital signs, including blood pressure and heart rate, are monitored frequently before, during and following the dosing session, as outlined in the MoP. Medications for cardiovascular emergencies are outlined in [Section 6.3.2](#). [Section 11.1.3](#) provides further details of AE reporting for blood pressure, heart rate, nausea, and headache.

10.1.2 Visual Perceptual Effects

Some people who have used serotonergic hallucinogens, such as psilocybin, experience persistent, distressing alterations in mostly visual perception that last from weeks to years after use (Espiard, Lecardeur, Abadie, Halbecq, & Dollfus, 2005). This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD). To date, however, no cases of HPPD have occurred in volunteers given psilocybin in contemporary research studies (Studerus et al., 2011). The risk of HPPD occurring after psilocybin administration can be reduced by screening participants for potential risk factors such as substance dependence and by excluding people reporting HPPD or other significant adverse events after prior use of hallucinogens.

Visual perceptual effects will be assessed as a solicited AE during Periods 3 and 4.

10.1.3 Drug Interactions

See [Appendix A](#) for a list of prohibited medications. Additional information is provided in the IB.

10.1.4 Pregnancy

There have been no human case reports or studies involving the effects of psilocybin on pregnancy. It is recommended that women who are pregnant avoid using psilocybin. See [Section 15](#) for pregnancy testing and results requirements.

10.2 Risk of Worsening MDD

An exacerbation of depressive symptoms including increased suicidal ideation could occur prior to or during the study. Participants in the study will be foregoing established treatments for depression while they are enrolled in the study. This risk of having a depressive exacerbation may be greater for participants in the niacin placebo group, as they will undergo a longer period of time without receiving a known active treatment. Although placebo interventions often have significant therapeutic benefits in patients with MDD, participants who receive niacin placebo may be at increased risk for worsening of depressive symptoms or development of active suicidal ideation with plan during the course of the study.

Study clinicians at each site will assume the role of mental health provider when a participant enrolls in the study through the final primary outcome time-point at post-dose Day 43. Monitoring for suicidality will be ongoing ([Section 11.1.3](#)). Study team members will inform a study clinician of any substantial worsening of depression or suicidality, or of any other concerns regarding a participant's health. Study clinicians will then assess the health and safety of this participant. If a study clinician decides that an antidepressant medication is warranted, or if the participant desires conventional treatment during or after the study, the study clinician will develop an appropriate treatment plan including referring the participant to an outpatient provider or to the clinician treating the participant prior to study entry.

10.3 Risks Associated with Collection of Potentially Sensitive Information

Sensitive information may be revealed during the screening process and/or during the course of the study. Identification of disease may occur during the screening process and may impact future insurability of the participant. In addition, some diagnoses can create stigmatization or self-stigmatization for the participant. Both the PI and participants may be at risk for a violation of privacy and/or loss of confidentiality. This risk will increase as the study progresses as ongoing health information will be collected.

Best practices will be followed at all stages of the study to ensure maximum protection in the collection, storage and usage of potentially sensitive information. All collected data will be stored on a secure electronic database coded by a study ID number and stored separately from any documents with personally identifiable information and/or a key that would link such information to study data. All research staff will complete human subjects training (per institutional requirements) to promote the proper conduct of scientific research in humans. Additionally, each study site will obtain a Certificate of Confidentiality (CoC) ([Section 13.11](#)).

10.3.1 Genetic Testing

The risks of collecting DNA samples and conducting genetic tests include:

- Personal stigmatization, discrimination or labeling if it is found that the individual has a form of a gene linked to a particular condition or trait
- Potential loss of or difficulty in obtaining employment or insurance either because of what the test results show with respect to the genetics of the tested individual or the genetics of an identified group with which the individual is associated because of a medical condition, ethnicity or social standing
- Group stigmatization, discrimination or labeling resulting from genetic inferences associated with certain medical conditions or certain ethnic or social groups

These risks will be reduced in this study by:

- Not disclosing results to participants
- De-identifying samples before genetic tests are conducted
- Limiting the number of individuals who have access to identifiable results
- Only retaining samples from participants that are randomized

10.4 Risks Associated with Psychiatric Questionnaires

The study psychiatric assessments may uncover strong and potentially disturbing feelings about the participant's past or present emotional state. While it is expected the risk for SAEs resulting from psychiatric assessments is very low, the likelihood of these risks occurring will be minimized by procedures described below.

Care will be taken to avoid bringing about undue psychological distress during the psychiatric interviews. This will be accomplished by using trained central and site raters and by collecting the "minimum necessary" information required for study purposes. In the event that a participant

becomes unduly distressed, a study clinician will be immediately contacted, and an appropriate clinical intervention plan will be developed.

10.5 Risks Associated with Venipuncture

The risks of drawing blood include discomfort, bruising, infection, bleeding and fainting. The amount of blood drawn during the study (approximately 20 mls) will not have any adverse physiological effects, nor will it lead to any long-term distress. Risks for blood borne pathogens from accidental needle stick and during sample processing exist. Not uncommonly a bruise may form at the puncture site.

To reduce risk of infection and bleeding standard sterile procedures for drawing blood will be used by certified personnel with extensive phlebotomy experience. To reduce the risk of fainting all participants will be asked about tendency to faint prior to venipuncture and will be placed in a recumbent position if they answer in the affirmative.

10.6 Contacting Emergency Services

Generally, if at any time during the study, including during your dosing session, study staff feel a participant is in danger of hurting him/herself or someone else then the study physician, PI and/or Lead Facilitator will be contacted immediately for further evaluation and follow up. In certain circumstances 911 may be called or the participant may be taken to the emergency room, including the following:

- If at any time during the study physician, PI and/or Lead Facilitator feels your situation is an emergency that requires immediate attention they will call 911 or the participant will be taken to the emergency room.
- If the participant becomes violent or aggressive during the dosing session and he/she does not respond to medications or calming by your session Facilitators, then the study physician, PI and/or Lead Facilitator may call 911, or the participant may be escorted to the emergency room.
- If the participant insists on leaving the research site before the dosing session is complete (they must remain on site for a minimum of 7 hours) and the study physician, PI and/or Lead Facilitator feels he/she is a threat to him/herself or others then they will call 911.
- If the study participant insists on leaving the research site before the dosing session is complete and the study physician, PI and/or Lead Facilitator do not feel he/she a threat to him/herself or others then they will call the support person previously identified to take the participant home.

If the study physician, PI and/or Lead Facilitator feels the participant may have a serious, but not urgent, psychiatric condition then he/she will be referred to his/her previously identified mental health provider, if one was identified, or to mental health services in the community.

10.7 Data and Safety Monitoring Board (DSMB)

A DSMB will oversee the safety monitoring for this study and will be comprised of experienced members with expertise required for overseeing the study. The DSMB will review protocol-specific reports, which will include an overview of the study objectives, actual and projected accrual, evaluation of patient demographics, and a summary of the number and seriousness of AEs. Cumulative reports of serious AEs requiring expedited reporting and any new serious AEs will also be reviewed per the DSMB plan. See the Study PSIL201 DSMB Charter for full details.

10.8 Abuse Liability

Like other psychoactive drugs, psilocybin is sometimes used in a manner that jeopardizes the safety or well-being of the individual or others (e.g., driving while impaired; a pattern of use that interferes with work, school, or relationships). Under such circumstances, psilocybin would be said to be *abused*. However, psychedelic medicines such as psilocybin are not typically considered drugs of *dependence* in that they do not engender compulsive drug seeking behavior (Johnson, Griffiths, Hendricks, & Henningfield, 2018; O'Brien, 2011), consistent with the observation that they are not reliably self-administered in nonhuman animals (Fantegrossi, Woods, & Winger, 2004; R.R. Griffiths, 1980; Poling & Bryceland, 1979). Further, they are not associated with a known withdrawal syndrome (O'Brien, 2011). Therefore, there is little risk that exposing human volunteers to psilocybin will leave participants physically or psychologically dependent on the compounds. In previous (R. R. Griffiths et al., 2011; R. R. Griffiths et al., 2006) and ongoing studies with psilocybin, exposing individuals with either no history of hallucinogen use or a history of minimal use (e.g., less than 10 times total and not within the last 5 years) in the context of a supervised and controlled research setting has not resulted in reported instances of subsequent illicit hallucinogen abuse. In the meta-analysis conducted by Studerus and colleagues (Studerus, Kommer, Hasler, & Vollenweider, 2011), the large majority of participants in psilocybin studies (approximately 90%) reported “no change” in their psilocybin use following their laboratory sessions, as well as “no change” in their overall drug consumption habits (e.g., use of alcohol, nicotine, cannabis, MDMA). Those who did report changes often described decreased consumption (see Table 5 in Studerus et al., 2011). Specifically, in terms of psilocybin use, more participants reported using it *less* often after their laboratory sessions (5.6% of all participants) than more often (3.3% of all participants).

10.8.1 Abuse Monitoring

Based on current information, it does not appear that psilocybin demonstrates signals associated with known abuse liability patterns when administered in a therapeutic setting under continuous observation in a single-dose session, for which further evidence will be collected in this study. Any abuse potential is further limited since the drug is not supplied to the participant to take home and is administered under careful clinical supervision in a restrictive setting. All clinical sites will comply with local and national requirements pertaining to clinical research with controlled substances. Each PI responsible for dispensation or administration of the investigational product will maintain current registration with authorities with oversight of controlled substances. Participants will never have the study drug in their possession or have access to it outside the closely supervised clinical setting, which removes the possibility of drug diversion (e.g., missing medication, loss of drug) or unrecognized non-compliance with

medication ingestion. While there is still a possibility of site drug diversion, this risk is mitigated through Drug Accountability process, documentation and monitoring. See [Section 8.6 Drug Deliver, Storage, Handling, and Accountability](#).

A CoC will be obtained to encourage study participants to be honest regarding addictive behaviors post-dosing. The following measures will be employed to monitor the abuse liability of psilocybin:

- Cases of noncompliance, protocol violations, participants lost to follow-up, and any other reasons why participants dropped out of the study will be assessed for signals of abuse
- Qualitative urine drug test data will be collected at Screening, Baseline and all post-dose assessments. Any positive findings that cannot be attributed to pre-approved concomitant medications or diet will be reviewed by the site medical clinician for evaluation and management.
- Prior lifetime illicit and non-prescription drug use will be collected at Screening via the Drug History Questionnaire and reassessed by self-report from Baseline to Randomization. Self-reported behaviors of alcohol and illicit and non-prescribed drug use will be collected via the AUDIT, DUDIT and SCID-CT at Baseline and Day 43/ End of Study, the Timeline Follow-Back will be used at Day 43/ End of Study to assess drug and alcohol use since dosing to characterize any illicit drug or alcohol use, including psilocybin, during that period. Additionally, urine drug screens, as described above, will be used to identify drug use during the study period. Behaviors will be compared before and after intervention in exploratory analyses. These measures will be used to provide objective data to assess the impact of single-dose psilocybin on addictive behaviors, not just in relation to non-study psilocybin use but also in relation to other addictive substances/behaviors.
- Drug overdose with suicidal intent will be captured as a solicited AE.
- Terms related to abuse liability appearing the MedDRA Preferred Terms will used to be classify abuse liability AEs as specified in [Section 11.1.1](#).

Additional detail regarding AE reporting related to substance or alcohol use is described in [Section 11](#).

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

An AE is any untoward medical occurrence in a research participant, whether or not considered drug related which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the PI is considered an AE.

Blood pressure (BP) and heart rate (HR) must meet one of the following criteria to be considered an AE for the purposes of this study:

- Systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg on three separate readings and requiring medication
- Clinically significant decrease in BP requiring medication
- Heart rate (HR) >100 beats per minute (BPM) and requiring medication
- Clinically significant decrease in HR requiring medication

The AE terms listed below are MedDRA Preferred Terms to be used in classifying adverse liability AEs when deemed appropriate by the PI (or designee):

- Euphoria-related terms: euphoric mood, elevated mood, feeling abnormal, feeling drunk, feeling of relaxation, dizziness, thinking abnormal, hallucination, inappropriate affect
- Terms of impaired attention, cognition, and mood: somnolence, mood disorders, and disturbances
- Dissociative/psychotic terms: psychosis, aggression, confusion, and disorientation

Evidence of substance or alcohol abuse, whether captured via one of the assessments in [Section 10.8.1](#) or via unsolicited self-report, will be reported as an AE only if it meets SAE criteria. Solicited AEs related to drug overdose are described in [Section 11.1.3](#).

11.1.2 Treatment Emergent Adverse Events

Treatment emergent adverse events are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment. Events with an onset after study drug administration will be considered TEAEs.

11.1.3 Solicited Safety Events

The following solicited AEs will be collected:

Visual perceptual effects (Periods 3-4) will be solicited by asking the following questions: 1) *Since your dosing session have you experienced any uncontrolled or disturbing return of study drug effects?*, and 2) *Since your dosing session have you experienced any visual distortions (e.g. geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified color, trails for images of moving objects, positive after-images, halos around*

objects)? If a participant reports “Yes” to any of the above questions a study psychologist or psychiatrist will follow up for further assessment/diagnosis.

Additional solicited AEs include:

- Active suicidal ideation identified through the C-SSRS and/or MADRS and verified by clinical assessment. (recorded for Periods 1-4; would result in [screen failure](#) or [early termination](#) in Periods 1-2)
- Headache (Period 3); and
- Nausea (Period 3); and
- Elevated blood pressure (BP) as defined by systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg on three separate readings and requiring medication (recorded for Periods 1-4; may result in [screen failure](#) or [early termination](#) in Periods 1-2); and
- Elevated heart rate (HR) as defined as >100 beats per minute (BPM) and requiring medication (recorded for Periods 1-4; may result in [screen failure](#) or [early termination](#) in Periods 1-2); and
- Drug overdose with suicidal intent (recorded for Periods 1-4; would result in [screen failure](#) or [early termination](#) in Periods 1-2).

Monitoring for suicidality will be ongoing throughout the duration of the study using the C-SSRS and MADRS. All participants who meet criteria specified in [Section 2.13.7](#) and [Section 2.12.1](#) will undergo further clinical evaluation. If at any time during an evaluation or follow up there is concern a participant is suicidal study staff will follow their institutional standard of care procedures for managing suicidality. General guidelines will also be provided in the MoP, which sites can utilize.

To assess for headache after psilocybin administration, participants will be asked if they have or experienced a headache during Period 3, and these will be classified as a migraine, tension headache, or other headache. On the dosing day, participants reporting headache will be encouraged to take non-steroidal anti-inflammatory agents or acetaminophen at home, if needed.

Visual perceptual effects, suicidal ideation verified by clinical assessment, headache, nausea, and overdose with suicidal intent will be reported through normal AE/SAE mechanisms.

11.1.4 Unsolicited Adverse Events

Any other observed and participant reported AEs and SAEs will be recorded for all study periods (Periods 1-4), following written informed consent. SAEs will be reported per FDA guidelines.

11.1.5 Suspected Adverse Reaction

Suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. A reasonable possibility implies that there is evidence that the drug caused the event.

11.1.6 Adverse Reaction

Adverse reaction is any AE caused by the drug. A Serious Adverse Event that is deemed to be caused by the drug is considered a Serious Adverse Reaction.

11.1.7 Serious Events (Serious Adverse Events, Serious Suspected Adverse Reactions or Serious Adverse Reactions)

An SAE or serious suspected adverse reaction or serious adverse reaction as determined by the PI or the Sponsor is any event that results in any of the following outcomes:

1. Death
2. Life-threatening AE (Life-threatening means that the study participant was, in the opinion of the PI or Sponsor, at immediate risk of death from the reaction as it occurred.)
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital abnormality or birth defect
6. Important medical event that may not result in one of the above outcomes but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

11.1.8 Unexpected Adverse Event

Any AE, the specificity or severity of which has not been previously observed. Observed/expected adverse events are those described in the IB. The determination of expectedness will be made by the Medical Monitor.

11.1.9 Suspected Unexpected Serious Adverse Reaction

Unexpected adverse reactions are considered suspected unexpected serious adverse reactions if the following three conditions are met:

1. The event must be serious (see [Section 11.1.7](#));
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose; and
3. The adverse reaction must be unexpected (see [Section 11.1.8](#))

11.1.10 Definition of Terms

Life threatening: A life threatening AE is defined as an event in which the participant is at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe.

Disability: A disabling AE is defined as a substantial disruption of a person's ability to conduct normal life functions.

Important Medical Event: Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.2 Guidelines for Assessing Intensity of an Adverse Event

The PI should use the following definitions when assessing Intensity of an AE:

- **MILD:** Participant is aware of symptoms or has minor findings, but tolerates them well and no or minimal intervention required
- **MODERATE:** Participant experiences enough symptoms or findings to require intervention
- **SEVERE:** Participant experiences symptoms or findings that require significant intervention

11.3 Guidelines for Determining Causality of an Adverse Event

The PI and Medical Monitor will use the following question when assessing causality of an AE due to the study drug or as a result of study participation: Is there a reasonable possibility that the study drug or procedure caused the event?

A reasonable possibility implies there is evidence that the specific event was caused by the study drug or as a result of participation in the study. An affirmative answer designates the event as a suspected adverse reaction, and the AE is therefore considered “related.” If the answer is no, then the AE is considered “unrelated.”

11.4 Actions to be Undertaken

The PI is responsible for the appropriate medical management of all AEs and for the personal safety and well-being of participants. In case of an AE, the PI will initiate appropriate treatment according to his/her medical judgment and will decide whether to withdraw the participant from the study.

11.5 AE Collection Period and Follow up

All AEs and SAEs will be monitored continuously during the study from the time of signing the ICF until the Day 43/ End of Study. SAEs will be followed until resolution, including post Day 43/ End of Study if warranted.

11.6 Medical Dictionary for Regulatory Activities (MedDRA)

AEs will be coded according to MedDRA, a clinically validated, standardized international medical terminology dictionary developed by the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

11.7 Site AE Reporting Procedures

Regardless of severity or relationship to the investigational product, all AEs occurring during the study must be recorded on the AE Case Report Form (CRF) set in the EDC.

- Description (medical diagnosis, if possible)
- Date of onset and resolution (if known when reported)
- Severity
- Assessment of relatedness to test article
- Action taken
- Outcome

If all information is not known at the time of initial reporting, an initial report should still be made. In the event there is a question as to whether the experience is serious, the information should be forwarded to the Medical Monitor for review. The PI is responsible for following up on completion of the SAE Form.

All serious events will be recorded on the SAE CRF set in the EDC data system within 24 hours of identification. If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection forms and electronically transfer (for example email) the information into the Study Coordinating Center and Medical Monitor. The site will enter the SAE data into EDC as soon as it becomes available.

The PI will conduct supplemental measurements and/or evaluations as medically indicated or as requested by the Medical Monitor or the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the PI will provide the Medical Monitor with a copy of a death certificate and any post-mortem findings.

New or updated information relevant to an AE or potential SAE will be recorded in the originally completed CRF and updated within 24 hours of the PI being aware of the new information.

Any serious event entered into the EDC will generate an automatic email notification to the site staff entering the data, Study Coordinating Center, Medical Monitor and the Sponsor.

The Medical Monitor will review all SAEs at the time they are reported and will determine whether the SAE must be reported to FDA/regulatory authorities on an expedited basis.

11.8 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be communicated to the IND Sponsor. The IND Sponsor or its representative will submit expedited safety reports (e.g. IND safety reports) to the regulatory agencies as necessary. Events that are serious, related and unexpected and result in death or a life-threatening event will be reported within 7 days, with

a follow-up report within 15 days. All other serious, related and unexpected events will be reported in 15 days to the regulatory authorities. The Sponsor will inform the PI of such regulatory reports (Investigator Safety Report). The site PI must submit safety reports as required by their IRB. Documentation of the submission and receipt by the IRB must be retained for each expedited safety report.

All serious events irrespective of their designation as “related” or “not related” to study product(s) will be reported to the FDA at least annually in a summary format in the IND Annual Report.

11.9 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an AE. A confirmed pregnancy in a participant (by urine or blood test) should be reported in the data system within 24 hrs of the PI being aware of the pregnancy.

The pregnancy should be followed until an outcome is known. (i.e., spontaneous miscarriage, elective termination, normal birth). All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, will not be considered as AEs, but will be captured on a pregnancy outcome form.

12 STUDY MONITORING, AUDITING AND DOCUMENTATION

The PI and the study team will be trained prior to the start of the study. The study sites will be monitored on site and remotely by monitors with the SCC. The site will be monitored as appropriate for the rate of enrollment in order to comply with GCP guidelines and to ensure validity of the study data. During each monitoring visit, consent forms will be reviewed, and source data verification will be performed to ensure compliance, including accurate and complete recording of data on CRFs, Source Records, and drug accountability records. A CRF collation supplied by the SCC will be completed for each participant randomized.

During or after the study, the regulatory authorities, the IRB, and/or representatives of the Sponsor may request access to all source documents, CRFs, and other protocol documentation for on-site audit or inspection.

All activities and responsibilities related to monitoring will be outlined in the study Monitoring Plan.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Study Conduct

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICFs, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the PI and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

13.2 Principal Investigator Responsibilities

The PI will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, Unanticipated Problems or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations

13.3 Human Subjects Training

All study staff, to include any individual interacting with a participant or who has access to participant data, will be required to complete mandatory human subjects training per local institutional requirements prior to interacting with study participants.

13.4 Financial Disclosure

PIs, co-investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. PIs, co-investigators and sub-investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study. The purpose of obtaining Financial Disclosure information is to minimize potential for bias.

13.5 Voluntary Participation

Participants will be informed, via the ICFs and the consent process, that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant would otherwise be entitled, and that the participant may discontinue participation at any time.

13.6 Benefits of Participation

There is no guarantee participants will receive a direct benefit from participating in this study. Study participation will include receiving a psychiatric and medical evaluation, including standard blood and urine-based safety laboratory tests. In addition, eligible participants will have a 50% chance of receiving an intervention (psilocybin) that has been reported in past studies to provide benefit for the treatment of symptoms. In addition, many individuals' depressive symptoms improve with placebo treatment.

Participants will have the chance to contribute to a scientific investigation, which may be of benefit to future patients, and may provide a sense of personal satisfaction in this regard. Benefits to others may include gaining significant knowledge regarding the potential utility of psilocybin for patients with MDD.

13.7 Alternatives to Participation

Potential participants may choose not to participate in this study. Individuals suffering with major depressive disorder (MDD), even when treatment resistant, have at their potential disposal a wide range of treatments and/or procedures that are viable alternatives to participation in the current study. These alternatives include:

- Pharmacologic treatments – a wide range of psychotropic medications have been studied for the treatment of MDD
- Somatic treatments - a variety of somatic treatments for MDD exist with various levels of evidence of efficacy and/or side effect profiles including ECT, repetitive transcranial magnetic stimulation (rTMS) and vagal nerve stimulation (VNS)
- Psychotherapeutic interventions - examples of psychotherapeutic interventions for which data are available include cognitive behavioral therapy, interpersonal psychotherapy and various forms of behavioral activation therapy
- Miscellaneous interventions - a wide range of behavioral and non-traditional interventions are in use for the treatment of depression including aerobic and strength-building exercise, meditation, acupuncture, yoga and massage

13.8 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. See [Section 7](#) for Premature Study Discontinuation procedures.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The PI may initiate study-site closure at any time, provided reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or PI may include but are not limited to:

- Failure of the PI to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate participant recruitment
- Discontinuation of further study intervention development

13.9 Vulnerable Populations

Prisoners, pregnant women and mentally impaired persons or any other individuals considered a Vulnerable Population will not be enrolled in this study.

13.10 ClinicalTrials.gov Registration

This study will be registered with ClinicalTrials.gov according to Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) regulations, which requires Applicable Clinical Trials to be registered within 21 days of enrollment of the first participant. In addition, the International Committee of Medical Journal Editors (ICMJE) and other journals require registration of clinical trials prior to enrollment of the first participant.

13.11 Certificate of Confidentiality

To further ensure the protection of participant data, upon IRB approval the PI at each study site will apply for a CoC through the FDA. With this CoC, the researchers cannot be forced to disclose information that may identify research participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The CoC cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the FDA. The CoC does not prevent the researchers from disclosing voluntarily, without a participant's consent, information that would identify them as a participant in the research project under the following circumstances: intent to hurt themselves or others. If this situation is an emergency, study personnel will call 911. In this situation, identifying information might be released to the appropriate authorities.

13.12 Cost to Participants

Aside from travel to and from the study site, there will be no costs to research participants for participating in this research study. As part of their study participation, study participants will receive study visits with labs/assessments, including medical and psychiatric screening,

preparatory sessions prior to dosing, dosing with psilocybin or active placebo, and integration sessions following dosing at no cost.

13.13 Participant Compensation

[Table 9](#) provides an itemized list of payment for study participation. Compensation will be prorated based on the extent of participation completed.

Table 9: Participant Compensation

Activity	Compensation
Screening and Re-Screening: Informed Consent (\$15); remaining Screening activities (\$35)	\$50
Baseline assessment	\$25
Preparation Sessions	\$50
Dosing session	\$100
Days 8, 15, 29 and 43 assessments (\$50 each)	\$200
TOTAL COMPENSATION	\$425

13.14 Treatment/ Compensation for Study Related Injury

The Sponsor will cover reasonable costs of treating a study-related injury if such costs are not covered by a participant's health insurance; Sponsor will not be responsible for such costs when injury is due to (a) negligence, recklessness or willful misconduct of Study site or investigators or site personnel or their failure to follow Protocol, applicable law or Sponsor instructions; (b) subject's non-compliance with Protocol requirements; or (c) natural disease progression or pre-existing disease. Some study-related injuries can be treated by the study physician, as described in [Section 6.3.2](#).

13.15 Protocol Deviations and Violations

All protocol violations and deviations must be addressed in study source and electronic documents, reported to the Sponsor, and must be sent to the site IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MoP.

13.16 Record Retention

The PI must retain all study records required by the Sponsor and applicable ICH-GCP and FDA regulations in a secure and safe facility. The PI must consult a representative of the Sponsor before disposal of any study records. Essential documents are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the Investigator Site File (ISF). All records must be retained until at least 2 years after the date a marketing application is approved by FDA for the drug for the indication for which it has been investigated or for 2 years after development of the drug is discontinued and the FDA is notified.

It is the responsibility of the Sponsor to inform the PI or institution as to when these documents no longer need to be retained.

13.17 Publication Policy

The Sponsor recognizes the importance of communicating medical study data and therefore encourages publications in reputable scientific journals and presentations at seminars or conferences. It is understood by the PI that the information generated in this study will be used by the Sponsor in connection with the development of the investigational product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the PI is obliged to provide the Sponsor with complete test results, all study data, and access to all study records. It is mandatory that all data analysis is done on the official monitored Sponsor database and that the analysis plan is agreed upon with the Sponsor statistician.

Any results of medical investigations with the Sponsor products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the PI and the Sponsor clinical research representative(s) prior to submission for publication or presentation. Due regard shall be given to the Sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patient protection, coordinating and maintaining submissions to health authorities, and coordinating with other ongoing studies in the same field.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the PI agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating PI will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

14 CONFIDENTIALITY AND DATA SECURITY

14.1 Confidentiality and Data Security at Research Sites

All participants will be seen in private rooms within a clinical or professional setting. Only the research coordinator, the Facilitators, and the participant will be present during the dosing session, with the exception of site PI and/or physician, as required.

Hard copies of study data will be kept securely, such as in a locked cabinet at each participating research site. Documents with identifiable information (including the informed consent) will be filed separately from coded study data.


Every effort will be made to strictly safeguard the confidentiality of participants in their role as research participants. Removing identifying information from data and restricting access to researchers and research teams directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. If past medical records are needed, participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. Any materials mailed to participants will be sent along with stamped return envelopes using the office address of the PI both as main and return address. All assessment records will be kept securely, such as in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers and research teams, study monitors, and individuals analyzing data.

Blood samples for biobanking and future analysis will be de-identified and stored securely throughout the study according to site-specific procedures. They will be coded in a way that does not include any direct identifiers. Participants will be given the option to consent to pharmacogenomic sample collection, which will not be required for entry into the study, and only those participants providing informed consent will have such samples collected. Additionally, only samples from randomized participants will be retained. Upon study completion, de-identified samples will be securely shipped to a central location for storage and/or testing. Samples may be stored for up to 15 years or the maximum duration allowed by the overseeing IRB.

As mentioned in [Section 13.11](#), a CoC will be obtained to protect the participants' privacy.

14.2 Advantage eClinical

The EDC platform used for this study will be Advantage eClinical developed and maintained by the Emmes Company, LLC. Advantage eClinical and the computing environment where it is deployed conform to the security requirements specified in the National Institute of Standards and Technology (NIST) Special Publication 800-18, "Guide for Developing Security Plans for Federal Information Systems," which provides guidance to contractors under the Federal Information Security Management Act of 2002 (FISMA), Public Law 107-347. Consequently, Emmes' Advantage eClinical is consistent with the requirements of the Office of Management and Budget (OMB) Circular A-130, Section 8b(3), "Securing Agency Information Systems."



Advantage eClinical is 21 CFR part 11 compliant.

14.3 Rebar

Rebar will develop the website using Rebar Recruit, a proprietary platform which enables efficient and secure digital patient engagement and recruitment. Data security is ensured by encrypting data in transit and at rest, limiting data access to authenticated users (and only to the extent necessary to complete tasks associated with a study), and employing additional software and physical safeguards. Rebar's approach to digital patient recruitment has been honed through years of crafting, implementing, and optimizing digital patient recruitment campaigns across a variety of indications and geographic regions. Rebar will develop content that complements the website design and is tailored to the needs of the study team and patient populations, while adhering to regulatory and legal constraints.

14.4 Signant Health (formerly Bracket Global)

The Signant Health platform, which includes the device that the sites and central raters will use, along with the servers and other databases, is 21 CFR part 11 compliant. Signant Health also has a Privacy Shield certification.

The computer-administered MADRS interview will involve a series of probe and follow up questions with multiple-choice response options. Each participant will respond to the computer prompts presented. The software places an unalterable time and date stamp on each report which cannot be modified, and the user's access to the study device is restricted to the participant-user interface. The study assigned participant ID is the only identifying information that is stored in the study device. The computer administered MADRS and other electronic outcome assessments (eCOA) completed on the study device will be encrypted and securely transferred to the central eCOA vendor, Signant Health. Study sites will have access to electronic records documenting the participant's computer-administered interview and other eCOA completed on the study device.

15 CORONAVIRUS DISEASE 2019 (COVID-19) MITIGATION

In recognition of the Coronavirus Disease 2019 (COVID-19) pandemic and in response to the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency, several measures have been implemented to mitigate the effect of COVID-19 on participant safety and trial integrity (see MoP for full details). Additionally, requirements for in-person study visits have been relaxed such that certain study assessments are allowed to be conducted remotely to minimize the length of the in-clinic visit and minimize physical contact between participants and clinic staff (see [Table 1](#)). The Sponsor and sites will continue to monitor the ongoing public health emergency and will evaluate the need for additional/fewer mitigation measures in accordance with local and institutional regulations.

16 PREGNANCY

16.1 Definitions: Women of Childbearing Potential (WOCBP)

All individuals who were assigned biological sex of female at birth, and who have had no change in biological sex regardless of gender identification, will be considered Women of Childbearing Potential and will be required to have documented method of birth control and undergo urine pregnancy testing. For the purposes of this protocol, they will herein be referred to as “women” for biological purposes only.

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomyNote: Documentation will be via self-report
3. Postmenopausal female
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
 - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

16.2 Contraception Guidance

16.2.1 Male participants

There are no restrictions on birth control choices/methods for male study participants.

16.2.2 Female participants

Women of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in [Table 10](#). Documentation of birth control method will be obtained at Screening and confirmed at all follow up visits. Changes in birth control method will be documented. If there was a lapse in birth control coverage, additional pregnancy testing may be warranted.

Table 10: Highly Effective Contraceptive Methods

<p>Highly Effective Contraceptive Methods That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly.</i></p>
<p>Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> • Oral • Intravaginal • Transdermal
<p>Progestogen only hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> • Oral • Injectable
<p>Highly Effective Methods That Are User Independent^a</p>
<p>Implantable progestogen only hormonal contraception associated with inhibition of ovulation</p> <ul style="list-style-type: none"> • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
<p>Vasectomized partner <i>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.</i></p>
<p>Sexual abstinence <i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i></p>

16.3 Pregnancy Testing

- All WOCBP who were assigned biological sex of female at birth and have had no change in biological sex regardless of gender identification, will be required to undergo urine pregnancy testing.
- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Pregnancy testing will be performed at Screening, Baseline, morning of dosing, Day 8, Day 43 and at any other time if it is suspected the participant may be pregnant.
- Pregnancy testing at all participating institutions will be conducted using a commercial urine dipstick.

16.4 Reporting Pregnancy Information

See [Section 11.9](#)

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Appendix A: Prohibited Medications

LIST OF PROHIBITED MEDICATIONS

Current use of any of the following medications will be grounds for exclusion. Current use is defined as the drug being last taken within five times the elimination half-life of the drug.

Drug Class or Name	Elimination Half life (T1/2) (hrs)	Required Medication Taper Duration ^a (Days)
Uridine Diphosphate (UDP) or Glucuronosyltransferase (UGT) Enzyme Modulators		
Atazanavir (REYATAZ®)	17	14
Diclofenac (topical diclofenac formulations are allowed)(VOLTAREN®)	6	14
Mycophenolic Acid (MYFORTIC®)	18	14
Quinidine (QUINAGLUTE®)	8	14
Ritonavir (NORVIR®)	5	14
Silybin	6	14
Valproate / Valproic acid (CONVULEX®)	16	14
Phenobarbital (LUMINAL®)	118	25
Antidepressants – Tricyclic/Tetracyclic		
Amitriptyline (ELAVIL®)	46	14
Amoxapine (ASENDIN®)	30(M)	14
Clomipramine (ANAFRANIL®)	24	14
Desipramine (NORPRAMIN®)	46	14
Doxepin (SINEQUAN®)	36	14
Imipramine (TOFRANIL®)	34	14
Maprotiline (LUDIOMIL®)	51	14
Mirtazapine (REMERON®)	40	14
Nortriptyline (PAMELOR®)	88	18
Protriptyline (VIVACTIL®)	92	20
Trimipramine (SURMONTIL®)	24	14
Antidepressants – SSRI/SNRI		
Citalopram (CELEXA®)	33	14
Desvenlafaxine (PRISTIQ®)	11	14
Duloxetine (CYMBALTA®)	12	14
Escitalopram (LEXAPRO®)	30	14
Fluoxetine (PROZAC®)	144	30
Fluvoxamine (LUVOX®)	26	14
Levomilnacipran (FETZIMA®)	12	14
Milnacipran (SAVELLA®)	8	14
Paroxetine (PAXIL®)	31	14
Sertraline (ZOLOFT®)	27	14
Venlafaxine (EFFEXOR®)	11 (M)	14
Antidepressants – MAOI		
Isocarboxazid (MARPLAN®)	Not reported	14
Phenelzine (NARDIL®)	12	14
Selegiline (ENSAM®, ELDEPRYL®)	24	14
Tranylcypromine (PARNATE®)	24	14

Drug Class or Name	Elimination Half life (T1/2) (hrs)	Required Medication Taper Duration ^a (Days)
Antidepressants - OTHER		
Bupropion (WELLBUTRIN®)	21	14
Mirtazapine (REMERON®)	40	14
Nefazodone (SERZONE®)	18	14
Trazodone (DESYREL®, OLEPTRO®)	24 (M)	14
Vilazodone (VIIBRYD®)	25	14
Vortioxetine (TRINTELLIX®)	66	14
Antipsychotics – Traditional		
Chlorpromazine (THORAZINE®)	35	14
Fluphenazine (PROLIXIN®)	24	14
Haloperidol (HALDOL®)	36	14
Loxapine (LOXITANE®)	8	14
Mesoridazine (SERENTIL®)	26	14
Molindone (MOBAN®)	Not reported	14
Perphenazine (TRILAFON®)	12	14
Prochlorperazine (COMPAZINE®)	8	14
Thioridazine (MELLARIL®)	24	14
Thiothixene (NAVANE®)	34	14
Trifluoperazine (STELAZINE®)	24	14
Antipsychotics – Atypical		
Aripiprazole (ABILIFY®)	68	14
Asenapine (SAPHRIS®)	24	14
Brexipiprazole (REXULTI®)	91	19
Cariprazine (VRAYLAR®)	21	14
Clozapine (CLOZARIL®)	105	22
Iloperidone (FANAPT®)	24	14
Olanzapine (ZYPREXA®)	70	15
Paliperidone (INVEGA®)	23	14
Pimavanserin (NUPLAZID®)	200 (M)	42
Quetiapine (SEROQUEL®)	7	14
Risperidone (RISERDAL®)	24	14
Ziprasidone (GEODON®)	10	14
Miscellaneous		
St John's Wort	20 (hyperforin)	14
S-adenosyl-methionine (SAM-e)	2	14
Efavirenz (SUSTIVA®)	76	15
Lorcaserin (BELVIQ®)	12	14
5-Hydroxytryptophan (5-HTP)	7	14
Cannabidiol (CBD)	60	14
L-Methylfolate (≥ 7.5 mg/day)	3	14
Lithium	36	14
Lamotrigine	29	14
Carbamazepine/ Oxcarbazepine	35/9	14

^a Calculated as the maximum of 5x the elimination half life OR 14 days.

(M) indicates the half-life of an active metabolite, when it is longer than that of the parent drug.

Prohibited Medications References

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Online Resources

DRUGDEX®

FDA Prescribing Information

Appendix B: Questionnaire Assessments

Acronym	Scale Name	Version	Draft Available?	Scoring Algorithm Available?
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment History Questionnaire	Signant Health modified (Lifetime)	Yes	NA
CGI-S	Clinical Global Impression - Severity	Modified w/ prompts	Yes	NA
C-SSRS – BL	Columbia Suicide Severity Rating Scale – Baseline	Baseline Screening	Yes	NA
C-SSRS – SLV	Columbia Suicide Severity Rating Scale – Since Last Visit	Since Last Visit	Yes	NA
EBI	Emotional Breakthrough Inventory	Electronic	Yes	Yes
HAM-A	Computed Administered Hamilton Anxiety Scale	Public Domain	Yes	NA
LICQ	Lifetime Illness Characteristic Questionnaire	Electronic	Yes	NA
Prompted-MADRS	Montgomery-Asberg Depression Rating Scale	Electronic; Prompted	Yes	NA
SMDDS	Symptoms of Major Depressive Disorder Scale	Version 1.0 ©2015 Critical Path Institute. All rights reserved.	Yes	
ODQ	Oxford Depression Questionnaire	Modified © Oxford University Innovation Limited, 2011.	Yes	Yes

Acronym	Scale Name	Version	Draft Available?	Scoring Algorithm Available?
		All rights reserved		
MEQ-30	Mystical Experience Questionnaire	Public Domain	Yes	Yes
Q-LESQ	Quality of Life Enjoyment and Satisfaction Questionnaire	Short Form	Yes	Yes
SCID-CT*	Structured Clinical Interview for DSM-5	Clinical	No	NA
SCID-5-PD*	Structured Clinical Interview for DSM-5– Personality Disorder	Clinical	No	NA
SDS	Sheehan Disability Scale	© Copyright 1983, 2010, 2012 David V. Sheehan. All rights reserved.	Yes	NA
DHQ	Drug History Questionnaire	© Sobell & Sobell, 2003	Yes	
AUDIT	Alcohol Use Disorders Identification Test	Electronic; Self-report	Yes	Yes
DUDIT	Substance Use Disorders Identification Test	Electronic; Self-report	Yes	Yes
TLFB	Timeline Followback	Public Domain	Yes	NA
FHS	Family History Screen	Copyright August, 1999 Myrna M. Weissman, Ph.D.	Yes	NA

*Per standard process for SCID, scale will be custom-designed in collaboration with copyright holder. Draft unavailable until developed. Once Usona formally approves acquisition of scale and the scale agreement is executed, the scale owner will initiate the customized draft.