A PILOT MECHANISTIC STUDY OF PSILOCYBIN-ASSISTED THERAPY AS A TREATMENT FOR DEPRESSION

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The Principal Investigator (PI), Ginger E. Nicol, MD is conducting the study and acting as the sponsor. As the Sponsor-Investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), as applicable.

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. Co-investigators and all research personnel, who are responsible for the conduct, management, and/or oversight of clinical trials, have completed Human Subjects Protection and ICH GCP Training.

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

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Investigator: _____
Ginger E. Nicol, MD

Signature: _____ Date: _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Pilot Mechanistic Study of Psilocybin-Assisted Therapy as a Treatment for Depression
Study Description:	This phase 2b pilot mechanistic study will evaluate the feasibility of conducting fMRI during psilocybin dosing in depressed adults, characterizing the acute and persisting effects of psilocybin-assisted therapy (PAT) on depression symptom severity and psychological flexibility, characterizing neural and proteomic indicators of treatment response with precision functional brain mapping (PFM) via functional magnetic resonance imaging (fMRI) and the senolysis-associated secretory phenotype (SASP) profile, a set of proteomic blood biomarkers associated with biological aging and depression treatment response. ***Up to 50 depressed adults*** will receive PAT as delivered in Phase II and III clinical trials of psilocybin for depression conducted by Usona Institute, involving 2-6 hours each of preparation and integration therapy before and following a facilitated dosing session with 25 mg of psilocybin. We will assess immediate (during dosing), acute (up to 1-week post-dose) and persisting (~30 days post-dose) effects of psilocybin on functional brain connectivity (FC) and SASP profile at two possible administrations. To examine the effects of psilocybin on FC at the individual level before, during and after acute psilocybin dosing, as well as up to a month post-dose, participants may undergo up to 10 fMRI sessions and up to 8 blood draws in Study Part A and up to 10 fMRI sessions and up to 7 blood draws in Study Part B. This pilot study is intentionally designed to estimate feasibility, safety, and preliminary signals of clinical and neurobiological change following psilocybin-assisted therapy. The study is not powered for confirmatory hypothesis testing. Analyses will emphasize estimation of effect sizes, confidence intervals, and operational feasibility metrics rather than formal statistical significance testing. Results are intended to inform the design, sample size planning, and endpoint selection of a future confirmatory trial.
Objectives:	**Primary Objectives:** Characterize ACUTE (~1-week post-dose) and PERSISTING (~30 days post-dose) effects of PAT in depressed adults at two possible administrations on: 1) Depression symptom severity (Montgomery-Asberg Depression Rating Scale [MADRS]). 2) Psychological flexibility (Multidimensional Psychological Flexibility Inventory [MPFI]).

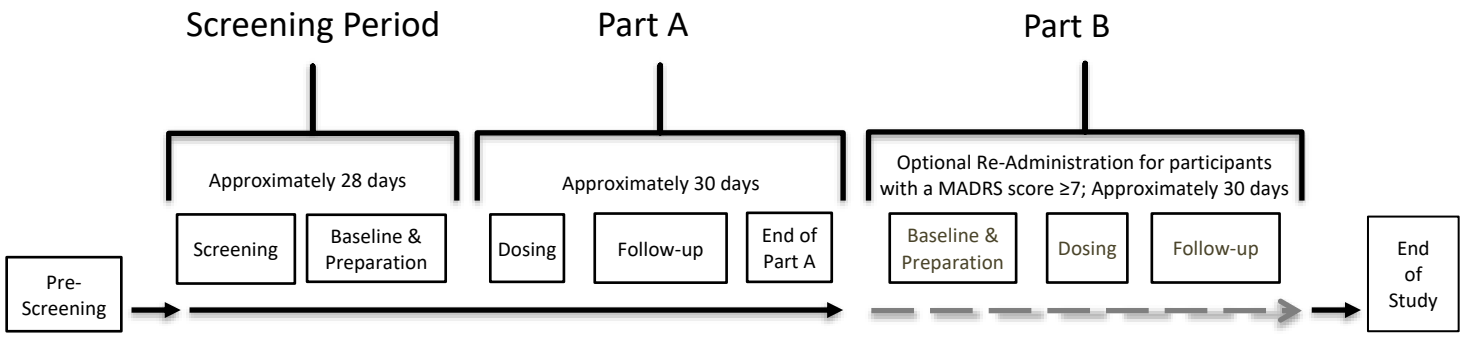
	Exploratory Objectives: 1) Characterize participants' subjective experience of PAT in the context of a clinical trial with the EMPATHY semi-structured qualitative interview developed by the research team and based upon Arthur Kleinman's explanatory model of illness. 2) Assess acceptability, appropriateness and feasibility of implementing PAT from the participant and researcher perspectives using validated process measures (AIM, IAM and FIM). 3) Characterize IMMEDIATE (during psilocybin dosing) and ACUTE (~1-week post-dose) effects of PAT in depressed adults at two possible administrations on: • Neural structure and functioning (structural, blood flow, extended resting state fMRI). • Proteomic blood biomarkers (SASP profile). 4) Characterize PERSISTING (~30 days post-dose) effects of PAT in depressed adults at two possible administrations on: • Neural structure and functioning (structural, blood flow, extended resting state fMRI). • Proteomic blood biomarkers (SASP profile). 5) Characterize PERSISTING (~30 days post-dose) effects of PAT in depressed adults at two possible administrations on: • Cognitive functioning (via selected NIH Toolbox Cognitive Function Battery [NIHT-CFB] tests of Executive Functioning [Dimensional Change Card Sort, Flanker Inhibitory Control and Attention], Working Memory [List Sorting] and Processing Speed [Pattern Comparison Processing Speed]).
Endpoints:	Primary Endpoints for Study Part A & Study Part B = Acute: 1 week (7 days) post-dose; Persisting: 4 weeks (28-30 days) post-dose Exploratory Endpoints for Study Part A & Study Part B = Immediate: during dosing; Acute: 1 week (7 days) post-dose; Persisting: 4 weeks (28-30 days) post-dose
Study Population:	The pilot trial population will include up to 50 individuals who are at least 18 years of age with mild to moderate depressive symptoms and who are otherwise generally healthy, are on a stable dose of an antidepressant monotherapy medication or are not receiving treatment for depression, and have no contraindications to treatment with psilocybin.
Phase:	2b
Description of Sites/Facilities Enrolling Participants:	This single site study will be conducted by the Healthy Mind Lab (HML) in the Department of Psychiatry, Washington University School of Medicine (WUSM), a part of Washington University in St. Louis (WUSTL). The lab has approximately 8,000 square feet of dedicated research space for clinical research, including offices, patient assessment rooms, and freezer storage. The laboratory has a particular emphasis on brain research. This is where patients will be consented, undergo clinical screening, behavioral and neurocognitive testing, and where clinical coordinators and research staff will be housed. The lab includes dedicated neuropsychological testing rooms, a medical exam room, and a psilocybin treatment room appointed according to multisite standards applied to Phase III clinical trials of psilocybin-assisted therapy for Major Depressive Disorder (MDD) and treatment-resistant depression (TRD) conducted by

	Usona Institute. The HML is also the physical home of the Washington University Center for Holistic Interdisciplinary Research in Psychedelics (CHIRP), and maintains regulatory and clinical trials infrastructure, including licensed clinicians who are trained in the delivery of psychedelic-assisted therapy in clinical trials conducted with psilocybin at Washington University. Neuroimaging will be conducted at the Mallinckrodt Institute of Radiology (MIR) at WUSM. The Neuroimaging Laboratories (NIL) consists of a group of investigators who share equipment and facilities necessary to do modern state-of-the-art neuroimaging research. The NIL is a major component of the Division of Radiological Sciences in the MIR at WUSM. NIL is in the East Building, a three-story facility across the street from the HML consisting of approximately 66,000 square feet devoted to imaging research and is designed to foster collaborative research among investigators.
Description of Study Intervention:	All eligible participants will receive approximately 20 hours of psychological support conducted by trained facilitators, including behavioral 'Preparation,' 'Integration,' and 'Dosing Day.' Drug: Psilocybin All eligible participants with depression who meet pre-defined MDD severity criteria (MADRS score ≥ 7) at Trial Day 30 Visit will be eligible to receive re-administration with open-label psilocybin 25mg, with psychological support and facilitation on dosing day as outlined above.
Study Duration:	5 years
Participant Duration:	The approximate total trial duration for each participant (from ICF signature) will range from 12-16 weeks, allowing adequate time and flexibility with participant, scanner, and MRI technician schedules, and including a repeat dosing period for participants who meet symptomatic criteria.

1.2 SCHEMA

The trial is summarized graphically below (Figure 1).

Figure 1: Schematic of the proposed clinical trial



1.3 SCHEDULE OF ACTIVITIES (SOA)

All participants will follow the PART A SOA #1 (**Error! Reference source not found.**). Participants who are eligible for open-label re-administration of psilocybin at the Day 30 visit will continue in the trial to follow PART B SOA#2 (

Table **1.2**).

Table 1.1: PART A - Schedule of Activities (SOA#1)

	Pre-Screening	Screening/Baseline Period					Dosing Day	Follow-Up								
														End of Part A		
	Phone Screen	Screening Visit	Entry Interview	Prep 1	Baseline MRI Scans	Baseline & Prep 2		Trial Day 2	1 Week Post Dose MRI Scans	Day 4 Phone Call	Trial Day 8	2 Week Post Dose MRI Scans	Trial Day 15	Trial Day 30 MRI Scans	Trial Day 30	Exit Interview[a]
			2 weeks prior to dosing	1 week prior to dosing	Within 7 days of dosing	1 day before dosing	Trial Day 1	Dosing Day +1	≤7 days of dosing	Trial Day 4 ±1 day	±1 day	±3 days	±2 days	±3 days	±3 days	≤7 days of Trial Day 30
Screening Instruments																
Verbal Consent	X															
Demographics and Contact Form	X															
Medication History	X															
PSQ	X															
PHQ-9	X															
Written Consent [b]		X														
HML Medical History Questionnaire		X														
ATRQ		X														
Inclusion/Exclusion Verification [c]	X	X				X	X								X[d]	
Safety Measures																
ConMeds/ AE recording [e, f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SPSEI							X	X			X				X	
Labs/Medical																
Height/Weight [g]		X													X	
Vitals (HR, BP, RR, Temp, O_2)		X				X	X[h]	X							X	
Physical Examination [i]		X														
Safety Labs (CBC, CMP, TSH)		X													X	
Urinalysis		X														
Urine Drug Screen [j]		X					X									
Urine Pregnancy Test [k]		X					X[l]								X	
ECG		X													X	
Proteomics		X				X	X				X		X		X	
MRI Questionnaire		X			X		X		X			X		X		
MRI					X		X		X			X		X		
Scales / Questionnaires [m]																
CIRS		X													X	
CGI-S		X													X	
CGI-I															X	
C-SSRS		X				X[n]	X[n]	X			X		X		X	
MADRS [o]		X				X		X			X		X		X	
SCID-5-CT		X														
CEQ - CR			X				X	X								
MPFI-24			X				X	X			X		X			X
PSS			X				X	X			X		X			X
NIH Toolkit						X									X	
MEQ-30								X								
CEQ - CH								X								
EMPATHY Interview			X													X
Facilitator Assessments																
Facilitator Approach Checklist				X		X	X	X			X		X			
Facilitator Preparation Checklist				X		X										
Dosing Day Monitoring Form							X									
Participant Release Evaluation							X									
Facilitator Integration Checklist							X	X			X		X			
Intervention Feasibility, Acceptability & Appropriateness															X	

[a] Participants will only complete Study Part A Exit Interview Visit if they receive a MADRS score of <7 at Trial Day 30, or are ineligible or unwilling to participate in re-administration. Participants who able, willing, and receive a MADRS score of ≥7 at Trial Day 30 are eligible to move to Study Part B and will move to Study Part B Re-Administration Baseline and Prep Visit.
[b] Enrollment occurs at the time the ICF is signed.
[c] Inclusion/Exclusion verification will occur at Screening and Baseline; eligibility confirmation will be ongoing until dosing, including confirmation of negative urine drug and pregnancy testing (for FOCBP only).
[d] Participants who meet re-administration criteria will proceed to the Re-administration Baseline Visit.
[e] Concomitant medications include the use of psychedelics and other substances. Any psychotherapy up to 3 months prior to Screening, as well as any changes in psychotherapy during the course of the trial (e.g., starting new therapy or changing the frequency or duration of psychotherapy), should be recorded.
[f] AESIs will be assessed through thorough assessments of AEs at each specified visit.
[g] Height will only be collected at Screening.
[h] Trial Day 1 vital sign assessments will occur pre-dose, no more than 1 hour before dosing. During the dosing session only BP and HR will be collected after IP administration. The method of body temperature assessment should remain consistent for each participant during the trial. Prior to discharge, BP, HR, RR, and body temperature will be collected at the end of the dosing day.
[i] Physical Exam to be performed at Screening only.
[j] Urine Drug Screen testing will occur at Screening and prior to dosing on Trial Day 1. Negative test results required prior to dosing. The Urine Drug Screen testing may be repeated, as needed.
[k] All FOCBP will be required to undergo pregnancy testing; documentation of birth control method for all FOCBP will occur at Screening and will be confirmed at each Follow-up visit.
[l] Pregnancy assessment occurs prior to dosing on Trial Day 1 (dosing). Negative pregnancy test results are required prior to dosing.
[m] The administration information for each scale/questionnaire is listed below:
Administered by Rater: CIRS, CGI-S, CGI-I, C-SSRS, MADRS, SCID-5-CT
Participant-facing: CEQ-CR, MPFI, PSS, NIH Toolkit, MEQ-30, CEQ-CH,
Clinical Interviewer: EMPATHY Interview
[n] The C-SSRS is to be the last assessment completed before participant release.
[o] The recall period for MADRS will be the last week (7 days), except at the Trial Day 2 assessment where the recall period will span from the administration of IP to the assessment time point.

Table 1.2: PART B - Re-Administration Schedule of Activities (SOA#2)

	Re-Administration Preparation and Baseline		Re-Administration Dosing Day	Re-Administration Follow-Up								
										End of Part B		
	Re-Administration Baseline and Prep	Re-Administration Baseline MRI Scans		Re-Administration Day 2	1 week post Re-Administration MRI Scans	Day 4 Phone Call	Re-Administration Day 8	2 Week post Re-Administration MRI Scans	Re-Administration Day 15	Re-Administration Day 30 MRI Scans	Re-Administration Day 30	Exit Interview
	Within 7 days of Re-Administration	Within 7 days of Re-Administration	Re-Administration Day 1	Re-Administration Day +1	≤7 days of Re-Administration	±1 day	±1 day	±3 days	±2 days	±3 days	Re-Admin Day 30 ±3 days	≤7 days of Re-administration Day 30
Safety Measures												
ConMeds/ AE recording [a,b]	X	X	X	X	X	X	X	X	X	X	X	X
SPSEI	X		X	X			X				X	
Weight	X										X	
Vitals (HR, BP, RR, Temp, O_2)	X		X[c]	X							X	
Abbreviated Physical Examination [d]	X											
Safety Labs (CBC, CMP, TSH)	X										X	
Urine Drug Screen [e]			X									
Urine Pregnancy Test [f]			X[g]								X	
Proteomics	X		X				X		X		X	
MRI Questionnaire		X	X		X			X		X		
MRI		X	X		X			X		X		
Scales / Questionnaires [h]												
CIRS	X										X	
CGI-S	X										X	
CGI-I											X	
C-SSRS	X[i]		X[i]	X			X		X		X	
MADRS [j]	X			X			X		X		X	
CEQ - CR	X		X	X								
MPFI-24	X		X	X								X
PSS	X		X	X			X		X			X
NIH Toolkit											X	
MEQ-30				X								
CEQ - CH				X								
EMPATHY Interview												X
Facilitator Assessments												
Facilitator Approach Checklist	X		X	X			X		X			
Facilitator Preparation Checklist	X											
Dosing Day Monitoring Form			X									
Participant Release Evaluation			X									
Facilitator Integration Checklist			X	X			X		X			
Intervention Feasibility, Acceptability & Appropriateness											X	

[a] Concomitant medications include the use of psychedelics and other substances. Any changes in psychotherapy during the trial (e.g., starting new therapy or changing the frequency or duration of psychotherapy) will be recorded.
[b] AESIs will be assessed through thorough assessments of AEs at each visit.
[c] Re-Administration Day 1 vital sign assessments will occur pre-dose, no more than 1 hour before dosing. During the dosing session only BP and HR will be collected after IP administration. The method of body temperature assessment should remain consistent for each participant during the trial. Prior to discharge, BP, HR, RR, and body temperature will be collected at the end of the dosing day.
[d] Abbreviated Physical Exam to be performed at Re-Administration Baseline only if there is an indication of physical status change.
[e] Urine Drug Screen testing will occur prior to dosing on Re-Administration Day 1. Negative test results required prior to dosing. The Urine Drug Screen testing may be repeated, as needed.
[f] All FOCBP will be required to undergo pregnancy testing; documentation of birth control method for all FOCBP will occur at Re-Administration Baseline and will be confirmed at each Follow-up visit.
[g] Pregnancy assessment occurs prior to dosing on Re-Administration Day 1 (dosing). Negative pregnancy test results are required prior to dosing.
[h] The administration information for each scale/questionnaire is listed below:
Administered by Rater: CIRS, CGI-S, CGI-I, C-SSRS, MADRS
Participant-facing: CEQ-CR, MPFI, PSS, NIH Toolkit, MEQ-30, CEQ-CH
Clinical Interviewer: EMPATHY Interview
[i] The C-SSRS is to be the last assessment completed before participant release.
[j] The recall period for MADRS will be the last week (7 days), except the Re-Administration Day 2 assessment where the recall period will span from the administration of IP to the assessment time point.

2 INTRODUCTION

2.1 STUDY RATIONALE

This trial is being conducted to evaluate the feasibility of conducting fMRI during psilocybin dosing in depressed adults, characterizing the acute and persisting effects of psilocybin-assisted therapy (PAT) on depression symptom severity and psychological flexibility, characterizing neural and proteomic indicators of treatment response with precision functional brain mapping (PFM) via functional magnetic resonance imaging (fMRI) and the senolysis-associated secretory phenotype (SASP) profile, a set of proteomic blood biomarkers associated with biological aging and depression treatment response. We will assess both acute and persisting effects of PAT on brain circuits using resting state FC and PFM. We will also assess change in the SASP, a panel of blood biomarkers of cellular aging.[1] Each participant will receive a single dose of psilocybin (25 mg) along with psychological support based on the Usona therapy protocol for the PSIL301 UAspire Phase III clinical trial of psilocybin for MDD and TRD, and up to 10 MRI sessions during the trial as outlined in the Part A Schedule of Activities #1 (**Error! Reference source not found.**). This trial follows the Phase II studies conducted by Usona (PSIL201 and PSIL201-LTFU)[2, 3] and COMPASS (COMP001 and COMP002)[4-7] which suggested that the antidepressant effect following a single 25 mg dose of psilocybin as monotherapy persists for up to 6 weeks and can persist for up to 12 months in some patients. However, relatively little study has been conducted on the safety and effectiveness of delivering PAT as augmentation to traditional serotonergic antidepressants (particularly, selective serotonin and norepinephrine reuptake inhibitors; SSRIs and SNRIs).[8, 9] Given the high rates of treatment resistance (approximately 30%) or partial treatment response (as high as 50% in some populations) in depression,[10] and the rapidity and magnitude of treatment response, and durability of treatment effect observed in prior clinical trials of PAT monotherapy, it is likely that far more patients will seek PAT as augmentation to their current antidepressant treatment than as a monotherapy. Thus, additional study is needed to fully evaluate whether and how treatment response to PAT might differ in people already taking serotonergic antidepressants. As individuals with persisting depression are likely to seek PAT as augmentation to ongoing depression treatment, the current mechanistic trial differs from the current Phase III clinical trials being conducted in MDD and TRD by Usona Institute and COMPASS Pathways, respectively, as the investigational product (IP, provided by Usona Institute's investigational drug supply program, cross reference IND: 129532) will be administered as open-label with permitted ongoing antidepressant monotherapy, with one possible re-administration available to participants with continued depressive symptoms.

This Phase 2b pilot mechanistic study is intentionally designed to evaluate feasibility and tolerability of conducting fMRI during psilocybin dosing and to generate preliminary estimates of clinical and neurobiological change following psilocybin-assisted therapy. The study is not powered for confirmatory hypothesis testing. Analyses will emphasize estimation of effect sizes, confidence intervals, data completeness, and operational feasibility (including imaging and biospecimen acquisition) rather than formal statistical significance testing. Findings will be used to refine procedures and inform endpoint selection and sample size planning for a subsequent larger, adequately powered trial.

2.2 BACKGROUND

Depression is the leading cause of disability worldwide, affecting an estimated 300 million people, and costing more per year than any other brain disorder.[11] Between 2015 and 2020, the percentage of adults with at least one major depressive episode in the past year remained stable, but prevalence in younger adults rose significantly, without commensurate increases in treatment-seeking.[12] Since 2002, the mortality rate from the most common mortality causes has declined or remained stable, while suicide-related mortality has risen by 30%.[13]

In general, treatment response, defined as a 50% reduction in symptom severity, is 40-50% for MDD and 10-20% in TRD.[14, 15] Novel therapeutics with a >50% response rate, particularly early in the course of illness, would result in approximately $30B in cost savings annually.[16] Although an earlier onset of TRD (defined as having two failed antidepressant trials of adequate dose and duration within the current depressive episode) may indicate a genetic predisposition to more severe illness in general, TRD is more commonly diagnosed later in life, when accumulation of allostatic load may uniquely contribute to a degenerative mechanism of treatment resistance. Chronological age has been proposed as a moderator of treatment response in depression, with older individuals experiencing more cognitive impairment than younger people, for example.[17] Despite available treatments, response rates remain modest and treatment resistance is common. These limitations highlight the need for therapeutics that act rapidly, produce durable effects, and target biological mechanisms not addressed by existing antidepressants.

Preclinical and early translational evidence suggests psilocybin may influence biological pathways related to cellular aging and neuroplasticity that are relevant to treatment resistance in depression. Psilocybin has been categorized as 'disruptive psychopharmacology' along with agents like ketamine, due to the rapid onset of antidepressant effects and sustained benefits with a single 25 mg dose. Psilocybin, a tryptamine, is often referred to as a "classic psychedelic" in that it acts as an agonist at serotonin 2 receptors, with particular affinity for the 2A (5-HT_{2A}) receptor.[18-20] Studies to date suggest geroprotective effects of psilocybin are multifactorial, impacting all three processes involved in cellular aging relevant to treatment resistance in depression[21, 22]: cellular senescence, telomere shortening, and DNA damage via oxidative stress and epigenetic changes. For example, psilocin (the active metabolite of psilocybin) increases SIRT1 expression in cells, a key regulator of senescence, mitochondrial function and neuroplasticity that is influenced by activation of intracellular 5-HT_{2A} receptors in cortical neurons.[23 24, 25] Serotonin 2A receptors are known to have immunomodulatory effects on cortisol release via interaction with the hypothalamic-pituitary-adrenal (HPA) axis, and 5-HT_{2A} receptor agonism is associated with reductions in Tumor Necrosis Factor-alpha (TNF-α).[26] Persistent reductions in interleukin-6 (IL-6) and C-reactive protein (CRP) have been reported after the acute effects of psilocybin have worn off.[27] Reduction of IL-6 and CRP by psilocybin has been suggested as a potential mechanism of action in depression.[28] In a more recent study, in vitro psilocin treatment (human lung and skin fibroblasts) was associated with reduced markers of cell-cycle arrest, increased markers of DNA replication and proliferation, and reduced SASP index, suggesting a role in decelerating or modulating the process of cellular senescence rather than directly eliminating senescent cells. In a complimentary in vivo study, aged female mice (19 months; roughly equivalent to 60–65 human years) were treated with vehicle or psilocybin once/month for 10 months (15 mg/kg). Psilocybin treated mice demonstrated significantly higher survival (80%), compared to vehicle (50%). Of note, though not quantitatively measured, psilocybin-treated mice in the study also exhibited phenotypic changes indicating attenuation of cellular aging as observed in better fur quality, hair growth and reductions in white hair in psilocin-treated mice compared to vehicle-treated mice.[29] These promising basic mechanistic studies have important implications for both prevention in younger individuals, where treatment resistance is more common, and treatment of older individuals, where symptom burden and morbidity lead to greater disability.[17] A clinical study in humans is warranted to identify optimized protocols for therapeutic efficacy of psilocybin, including the age of treatment initiation, treatment frequency and dose, and to determine whether mechanisms of treatment effect differ based on biological age.

Premature cellular aging is a potential mechanism of treatment resistance in depression. Numerous studies have characterized biological abnormalities in depression that are linked to accelerated aging. These include epigenetic aging via DNA methylation, which has been associated with increased biological age and mortality in depressed individuals,[30] and shortened telomere length, reflecting genomic instability and bioenergetic capacity, which together can cause irreversible cellular senescence. Other mechanistic drivers of cellular aging that are relevant in depression include inflammation, hormonal changes, and FC in brain networks that are present/measurable even in youth/prior to illness onset. In the NIH-funded Biotype-Assisted Augmentation Approach in Resistant Late Life Depression study (BAARD, UG3MH137353, PI

Nicol), we have developed a computational model based on cognitive, clinical, neuroimaging and proteomic data (via the SASP biomarker profile) to simulate antidepressant treatment response using depression biotypes based on known pathophysiology of depression and aging – neuroinflammation, neurovascular compromise and cellular senescence.[31-34] While these mechanisms seem exclusive to aging populations, it's worth noting that younger individuals with early onset of severe mental illness, including depression, have high levels of inflammation and related signs of biological degeneration measurable prior to treatment initiation, suggesting a target for prevention.[35] These findings support a framework in which accelerated biological aging contributes to treatment resistance in depression. Interventions that modulate cellular aging and neuroplasticity may therefore represent a novel mechanistic strategy for improving outcomes.

Psilocybin as a mechanistic probe for understanding treatment response in depression. Cognitive flexibility is the capacity to inhibit a dominant response when it represents a non-optimal or inappropriate solution to a problem. During stress, the likelihood of the dominant, nonflexible response increases as does the delay in providing the flexible or novel response. *Stress is also associated with* retraction of apical dendritic arbors *in the frontal cortex*, an indicator of *neuroplasticity.*[36] Cognitive flexibility is impaired by serotonin depletion in the prefrontal cortex *and can be modulated by 5-HT_{2A} receptor antagonism in animal models,*suggesting 5-HT_{2A}-mediated cell signaling as a transdiagnostic mechanistic target. Resting state FC measured via fMRI is a useful tool for studying the acute and latent effects of 5-HT2A agonism on human brain networks. FC measures coherent fluctuations in blood oxygenation level dependent (BOLD) signal over time between widely distributed brain networks. Studies of classic psychedelics using FC have shown an acute decrease in connectivity throughout the brain and in particular in the default mode network (DMN),[38-40] which correlates with hallucinogenic effects. The DMN is a collection of highly connected brain areas, including the subgenual cingulate, medial prefrontal cortex, posterior cingulate cortex, inferior parietal cortex, and parahippocampal cortex, involved in self-awareness, autobiographical memory and implicated in depression.[41] The subgenual anterior cingulate cortex in particular has been implicated in emotional processing and is hyperactive in depression and anxiety.[42] Recent methodological advances in neuroimaging have enabled the measurement of brain connectivity in individual participants with high precision and accuracy, an approach referred to as PFM. PFM consists of structural, task, blood flow, and repeated resting state fMRI incorporating extended image acquisition (>100 minutes of resting state per participant), aggressive data cleaning, and analyses designed to examine treatment-related change in FC at the individual level. PFM has demonstrated clear neuroscientific and translational advantages over standard imaging approaches for capturing changes that correspond to neuropsychiatric measures of behavior.[43, 44] For example, PFM has been used to study the effects of temporary arm immobilization (casting) on brain plasticity with daily imaging. In that study, large magnitude changes in FC and 'plasticity pulses' in motor and action control areas were observed during the casted period.[44] In a more recent, groundbreaking study of the effects of psilocybin on brain function, we observed massive global disruption of FC in healthy young adults treated with 25 mg of psilocybin.[45] We also observed treatment-related changes within and between brain networks relevant to depression, including in the DMN, salience network (SN), and Central Executive Network (CEN), and within-individual effects correlated with the mystical experience, which is associated with therapeutic response to psilocybin.[45, 46] Thus, we plan to extend these observations into older adults with depression. A general decline in network segregation is observed with increasing age.[47, 48] The proposed experiments will clarify how the complex relationship between network segregation and age relates to depressive illness and may be a relevant biomarker of illness severity and treatment response.[49-51] Precision functional brain mapping provides a quantitative framework for linking acute pharmacologic effects of psilocybin to individual-level changes in brain network organization that may predict clinical response.

Summary of clinical trials to date evaluating single-dose psilocybin (25 mg) in depressed adults. Clinical development programs evaluating single-dose psilocybin have demonstrated a favorable safety profile and clinically meaningful antidepressant effects in both healthy volunteers and patients with

depression. Two organizations have conducted and/or are conducting clinical trials of psilocybin in adults with depression: COMPASS Pathways and Usona Institute. The results of completed trials are summarized below.

COMP002, a Phase I, healthy volunteer study (N=89), found that 25 mg and 10 mg doses of COMP360 (COMPASS Pathfinder Limited's [COMPASS] proprietary synthetic psilocybin formulation) were generally well-tolerated and did not have any detrimental short- or long-term effects on cognitive functioning or emotional processing compared to placebo. In total, 511 treatment-emergent adverse events (TEAEs) were reported over a 12-week duration. There were no deaths, no serious TEAEs, and no TEAEs led to study withdrawal. The most frequently reported TEAEs were headache (n=63, 27.0%), insomnia (n=33, 14.2%), nausea (n=29, 12.4%), and fatigue (n=24, 10.3%). The majority of TEAEs were of mild to moderate severity, and treatment-emergent serious adverse events were reported for 12 participants (5.2%).

COMP 003, an open-label, Phase II exploratory study (N=19) was conducted to assess the safety and efficacy of COMP360 25 mg *as an adjunct to selective serotonin reuptake inhibitor (SSRI) therapy* in adults with TRD. Overall, 17 TEAEs were reported by 12 participants (63.2%) over the 3-week study duration. The majority of TEAEs were of mild to moderate severity and resolved within a week of onset. COMP 001, a Phase IIb, international, multicenter, randomized, double-blind, controlled, dose-finding study (N=233), was conducted to assess the safety and efficacy of two different single doses of COMP360 25mg and 10mg versus 1mg, delivered as monotherapy with psychological support for TRD. The primary efficacy endpoint, comparing change in MADRS total score from baseline to week 3 between the 25 mg treatment group and the 1 mg treatment group, showed a statistically and clinically significant treatment difference of -6.6 points ($p<0.001$), observable within 24 hours of dosing and persisting for up to 6 weeks following dosing. A non-significant treatment difference of -2.5 points was observed between the 10 mg and 1 mg treatment groups at Week 3.

PSIL102-TQT, a Phase I double-blind, single dose, randomized, placebo- and positive-controlled, 4-treatment, 4-period, 12-sequence crossover design was conducted in 36 healthy volunteers, evaluating single psilocybin doses of 0.3, 0.45 and 0.6 mg/kg (or up to 42 mg in a 70-kg participant). The percentage of participants who experienced at least one TEAE was similar during the psilocybin 25 mg (71%) and psilocybin 50 mg (81%) treatment periods. There were no participants with clinically significant ECG findings during the study, and no increases in QTcF to ≥500 msec. All doses were otherwise well tolerated, and dose strength was not correlated with adverse event (AE) frequency. PSIL201, a Phase II randomized, double-blind, placebo-controlled clinical study, 25 mg psilocybin was compared with 100 mg niacin (active placebo) in 104 participants with MDD and moderate to severe depressive symptoms. The study met the primary endpoint and key secondary endpoint; greater improvements in depressive symptoms assessed by central-rater MADRS score were observed in the psilocybin group compared to the niacin group starting at Day 8, and this effect was sustained until Day 43. These findings (improvement with psilocybin vs niacin) were consistent across different depression scales as well as scales measuring functional disability, anxiety, and quality of life. There were no deaths, no treatment-emergent SAEs, no AEs leading to study discontinuation, and no cardiovascular AEs. On dosing day, the most frequently reported TEAEs in the psilocybin group were mild to moderate in severity and included headache, nausea, and illusion. From Day 2 through the end of study, the most frequently reported TEAEs in the psilocybin group were headache and depression.

In addition to the above studies, two large-scale Phase III clinical trials of psilocybin in MDD and TRD are currently being conducted by COMPASS and Usona, and thousands of participants have received psilocybin in more than 100 smaller clinical trials for various clinical indications, including depression, anxiety, eating disorders, substance use disorders, and trauma-related disorders.[52-54] The most commonly reported adverse experiences reported in these completed clinical trials were psychological in nature

(anxiety, paranoid/delusional thinking). The most reported physical AEs involved cardiovascular effects (increased blood pressure and heart rate), nausea and headache.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 POTENTIAL RISKS ASSOCIATED WITH STUDY MEDICATION

Overall, the most commonly reported AEs associated with psilocybin administration in published studies are disorientation, lethargy, euphoria, emotionality, religiosity, visual hallucination or illusions, anxiety; physiological changes including pupil dilation, increased heart rate (HR), changes in blood pressure (BP), tremor (25%), dysmetria (16%).[55] Nausea (may occur in 44% of individuals after ingesting psilocybin mushroom,[56] but only 8-14% after ingesting purified psilocybin.[57] Less likely AEs are transient moderate-severe anxiety (17-33%; versus 15% in placebo, headache following resolution of acute effects (13-33%; typically, the following evening). Rare AEs are severe anxiety or paranoia (0-3% in clinical studies), fear/panic, distress, dysphoria. Distressing and dysphoric effects including sensory (frightening hallucinations or illusions), somatic (disturbing hyperawareness of physiological processes), and psychological (e.g. troubling thoughts or feelings).

Some people who have used serotonergic psychedelics, such as psilocybin, experience persistent, distressing alterations in mostly visual perception that last from weeks to years after use.[58] This condition is diagnosed as hallucinogen persistent perception disorder (HPPD). In studies involving cancer patients examining cancer-related anxiety and depression, no cases of HPPD were identified, and no participants developed any symptoms of paranoia or anxiety that required pharmacological intervention or anything more than reassurance from session facilitators. In Study PSIL201, one participant experienced visual perceptual effects after the psilocybin intervention lasting for 11 days post-dose; the participant reported mild motion in their field of vision but reported these effects to not be disruptive in the participant's daily activities. The visual perceptual effects resolved spontaneously and were not considered indicative of a risk of hallucinogen-persisting perception disorder. Other participants who experienced visual perceptual effects after the day of drug administration (n=3) had effects lasting one to four days. The risk of HPPD occurring after psilocybin administration may be reduced by screening participants for potential risk factors such as substance dependence and by excluding people reporting HPPD or other significant AEs after prior use of psychedelics.

Importantly, psilocybin has exceptionally low dependence potential and low lethality (active/lethal dose) in comparison to most other psychoactive drugs.[59, 60] In studies that provided adverse events data no severe adverse events were noted.[39, 57, 61] These studies specifically noted that no participants experienced persisting psychosis. One study also noted that no participants abused or became addicted to psilocybin.[57] See the USONA Investigator Brochure for additional information (Appendix A).

2.3.1.2 POTENTIAL RISKS ASSOCIATED WITH STUDY ASSESSMENTS

Behavioral Assessments

There are no physical risks associated with study assessments to obtain psychiatric and medical history, to evaluate psychological, cognitive and behavioral symptoms, and ascertain participants' perception of illness and experience of participating in research. Some participants may find the questions to be boring or difficult to answer and thus mildly distressing. Minimal risks exist for the collection of sensitive information on participants. The assessments to be conducted as part of this study involving mood assessments, neuropsychological testing, and behavioral and functional assessments are non-invasive and carry with them no more than minimal risk. The most significant risk to participants related to research

assessments are those that would follow a breach of confidentiality and the disclosure of clinical information.

Blood Draws

Collecting a blood sample from a vein might cause pain, swelling, bruising, lightheadedness, fainting, and very rarely clot formation, nerve damage, and/or infection at the site of the stick.

Electrocardiogram

Electrocardiogram stickers on participant's skin may cause local irritation.

MRI Scans

The potential risks of magnetic resonance imaging (MRI) scanning include more common risks of discomfort inside the MRI scanner ("claustrophobia") and muscle stiffness from lying still. It is possible to experience muscle cramping caused by nerve stimulation or tissue heating, which may cause a feeling of warmth. Very rare risks include hearing loss due to the loud hammering noise from the MRI scanner, sensation of flashing lights while in the MRI scanner, burns that could be serious. Individuals with a device such as a pacemaker, bone hardware, cardiac stent, or device placed in the uterus may have additional risks. These risks could include heating or movement of the device, device malfunction, or damage to the tissue that surrounds the device. Devices that are viewed as not MR compatible on review would be contraindicated for the study.

2.3.1.3 OTHER POTENTIAL RISKS

There is a risk that data may be accidentally disclosed outside of the study. There is a risk for the identity of a participant to be disclosed to non- study personnel, resulting in a loss of privacy and a potential risk to reputation. This risk is estimated to be extremely low due to the various protections listed below.

There are also risks to participants inherent to the diagnosis of depression. Depression can negatively impact all aspects of a participant's daily life and may result in problems at home, school, or work. In addition, participants with depression may be at increased risk of suicidal ideation or behavior. The clinical care provided to participants in this study involves a higher level of clinical observation and intervention than is the current standard of care, and the treatment under study thus far has demonstrated low risk of exacerbating or unmasking suicidal thoughts or behavior and may be effective in reducing suicidal ideation in depressed populations. Nonetheless, people with depression are at increased risk for suicidal thoughts, and this will be carefully monitored throughout study participation.

2.3.2 KNOWN POTENTIAL BENEFITS

Psilocybin is currently being studied in clinical trials for depression, obsessive compulsive disorder, substance use disorders and eating disorders. Current evidence from psilocybin trials suggests that a single 25 mg dose of psilocybin can induce antidepressant effects that persist for at least 6 weeks and for at least 12 months in some patients. In addition, participants in these trials have experienced essentially the full magnitude of treatment effect within the first week following psilocybin administration, suggesting that patients may obtain relief from their depressive episode more quickly than with traditional oral antidepressants.

This study will employ a brain imaging technique referred to as PFM, which involves extended fMRI acquisition, aggressive data cleaning approaches, and analyses designed to examine FC at the individual level during exposure to psilocybin to precisely examine 5-HT2A receptor agonism effects on brain networks and blood biomarkers to measure markers of cellular senescence and aging, the senescence-associated secretory phenotype (SASP). The results of this study may have broad applicability to human health and disease, enabling innovative studies of disruptive pharmacology as a treatment paradigm with

applicability in a variety of conditions that are adversely impacted by accelerated aging. Psilocybin is unique in mechanism from currently approved psychiatric medications; however, the neurobiological effects and therapeutic mechanism are not yet well understood.

These benefits outweigh the minimal risks involved in this protocol.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

2.3.3.1 PROTECTION AGAINST POTENTIAL RISKS ASSOCIATED WITH STUDY MEDICATION

To ensure the safety of participants, the investigational product (IP) will be administered in a controlled setting alongside psychological support provided by trained Facilitators. Psychological support is comprised of 1) a period of preparation with Facilitators prior to dosing; 2) administration of IP in an aesthetically pleasing room under the supervision of 2 Facilitators; and 3) post-dose integration sessions during which participants will discuss their dosing experience with the Facilitators.

Drug administration will take place in the HML at the WUSM campus, in a dedicated neuropsychological testing room modified specifically for this study. The participant will be under observation by two trained study facilitators for at least 7 hours following study drug ingestion. A clinician will be on-call should any serious adverse event occur.

Safety of the psilocybin dose has been determined based on extensive previous research to avoid unwanted effects. Psilocybin has been determined to achieve optimal efficacy with minimal adverse events at a fixed dose of 25 mg.[62, 63] Additionally, steps to mitigate adverse events (including preparing participants for possible thoughts/effects they may experience, providing a calm/comfortable environment, emesis basin, continuously monitoring for safety by a trained monitor, and having rescue medications available) will be implemented based on best-practice safety recommendations for psilocybin research.[64]

During Screening, an electrocardiogram (ECG), resting BP, HR, respiratory rate (RR), oxygen saturation (O2), a medical history, and physical examination will be conducted to evaluate for any medical signs or conditions that are contraindications for psilocybin exposure.

Two trained facilitators will be present during the psilocybin dosing session to continuously observe and evaluate the participant's physical and mental status. Participants will have HR, BP, RR, and psychological state routinely monitored throughout drug sessions. Cardiovascular monitoring will consist of HR and BP monitoring prior to dosing (baseline), and at 30, 60, 90, 120 minutes, 4, 6, and 7 hours after drug administration. Prior to dosing, BP must measure $\leq$140/90 mmHg to treat. Clinical/safety ratings will be done prior to completion of each session to assure that participants have returned to their "baseline" prior to discharge from the research unit.

In rare cases, psilocybin can cause severe anxiety or paranoia (0-3% in the research setting) that is not redirectable with psychological support. As an added safeguard, the study clinician will have immediate access to atypical antipsychotic and benzodiazepine medications that can be used as needed for extreme paranoia or anxiety. Participants will not be discharged until after the 7-hour BP and heart rate assessments have been completed. A licensed study clinician will either be present during the dosing session or on-call throughout the duration of the dosing session and will need to be available to be onsite within approximately 15 minutes in the event of a physiological or psychiatric emergency for medical/psychiatric assessment. The study clinician is responsible for administering rescue medications (see Section 6.5.3 for list of allowable rescue medications by indication), should these be warranted. Anyone reporting extreme paranoia, headache, dizziness, or any other serious untoward effects during or after drug exposure will be

evaluated by a study clinician for a safety assessment to monitor their vitals and medical status. After evaluation by a study clinician, participants experiencing serious adverse events may be excluded from the study and their participation terminated.

2.3.3.2 PROTECTION AGAINST POTENTIAL RISKS ASSOCIATED WITH STUDY ASSESSMENTS

This project will be conducted at the HML in the department of Psychiatry and the MIR at WUSM and will abide by all Federal Regulations related to human subject protection, inclusion of women and minorities, and privacy of individually identifiable health information. All study personnel will undergo training specific to the use of human participants in research (CITI), will be HIPAA and GCP trained, and will be approved by the Washington University in St. Louis Institutional Review Board. Throughout the study, we will confirm plans to assure: 1) accurate, complete, and verifiable data collection and 2) the rights and well-being of human subjects will be protected, in accordance with 45 CFR 46 (Protection of Human Subjects) and, as applicable, 21 CFR part 50 (Protection of Human Subjects).

The risks of breaching confidentiality will be strictly limited using the HIPAA "two lock" policy and access to data. Additionally, study ID numbers will be used rather than participants' names in the database created for this project, and the data will be restricted to study personnel. No identifiers will be included in any computer files or reports generated by this study.

Participants will be assured that participation in the study is completely voluntary, and that they are free to withdraw consent at any time and discontinue participation without prejudice to their current or future medical care. The objectives of the project, all requirements for participation, and any possible discomforts and risks will be clearly explained at each contact to the participants orally and in writing. All participants must sign an informed consent form, indicating their consent and/or assent, approved by the WUSM IRB, before they can participate in the study.

During the screening process, participants will be questioned in detail about any medical or work history that might indicate the presence of any metal object in their body and screened for any surgical procedure or operation that might have result in the placement of metallic foreign bodies or devices (e.g., pacemakers, aneurysm clips, cardiac defibrillator, neurostimulator, etc.), following the same guidelines used for clinical studies in the MIR. All individuals having contact with patients for the purposes of the fMRI study have passed a safety examination created by the NIL-RC at MIR to ensure that participants are properly trained to screen participants. FDA-approved clinical MRI pulse sequences will be used. There are software protections on these systems that prevent the operation of investigational MRI pulse sequences that exceeds the FDA limits on RF power. The development of muscle aches and pains associated with lying still in the scanner for long periods is minimized by providing appropriate cushions at pressure points and beneath the knees as desired by the participant. To reduce scanner noise, participants are provided with earplugs and a noise-reducing headset. Participants are informed that if they cannot tolerate the noise from the MRI-scanner they can ask to end the session at any time. The appearance of claustrophobia on entering the scanner will result in termination of the experiment. Participants and clinical research facilitators can communicate with one another through a dual-microphone system that is active during the entire scan. If participants experience discomfort or claustrophobia, they can tell the facilitator or MRI technician and will be removed from the scanner immediately. After each run, the MRI technician establishes verbal contact with the participant to monitor level of comfort and consent to continue the MRI scanning.

If the imaging technician observes substantial brain lesions or structural abnormalities on the MRI, the images will be reviewed by a study clinician, and the participant will be notified. A copy of the non-clinical imaging will be provided to the participant's physician if requested.

2.3.3.3 PROTECTION AGAINST OTHER POTENTIAL RISKS

2.3.3.3.1 SUICIDE RISK MONITORING AND MANAGEMENT FOR PARTICIPANTS WITH MDD

Suicide is not a risk of the study per se but is a risk of major depression that we aim to mitigate via the treatment and close monitoring offered in this clinical trial. Participants' absolute risk for completing suicide during this study remains very low (i.e., about 1 in 3,000 to 10,000) and participation in the study does not create or increase the risk of completed suicide; rather, treating depression is one of the most efficient ways to decrease suicidal risk in older depressed individuals. Nevertheless, since the rate of completed suicide in the US is about twice the rate of homicide, and most individuals who complete suicide suffer from depression, all participants have increased suicide risk. To mitigate this risk and prevent deaths by suicide:

- Patients who have suicidal ideation to the extent that inpatient care is appropriate will be excluded from the study and referred for acute psychiatric evaluation and care.
- Risk for suicide will be formally assessed at every study visit for the duration of the study, and an emergency contact and/or contact information for their primary care provider will be obtained for all participants.
- If a participant becomes acutely suicidal, the study team will activate emergency medical services and engage the emergency contact and/or medical providers. A study team member will stay with (or on the phone with) the participant until help arrives.
- In case of extreme emergency, research staff are instructed to call their hospital security team, 911 (or 988 if available) for immediate help and/or escort the participant to the nearest emergency department for further safety evaluation.

The degree of distress for participants enrolled in this trial is considered acceptable in view of the full risk-benefit profile. Participant safety will be monitored throughout the trial as per Section 8.6.

3 OBJECTIVES AND ENDPOINTS

Table 3: Study Objectives and Related Endpoints

OBJECTIVES	ENDPOINTS
Primary	
Characterize the ACUTE (~1-week post-dose) effects of PAT at two possible administrations on depressive symptom severity measured via the MADRS total score	• Change from Study Part A Screening/Baseline Period to Trial Day 2 Visit and Trial Day 8 Visit in MADRS total score • Change from Study Part B Baseline to Re-administration Day 2 Visit and Re-Administration Day 8 Visit in MADRS total score
Characterize the ACUTE (~1-week post-dose) effects of PAT at two possible administrations on psychological flexibility measured via the MPFI	• Change from Study Part A Screening/Baseline Period to Trial Day 8 Visit in MPFI score • Change from Study Part B Baseline to Re-Administration Day 8 Visit in MPFI score
Characterize the PERSISTING (~30 days post-dose) effects of PAT at two possible administrations on depressive symptom severity measured via the MADRS total score	• Change from Study Part A Screening/Baseline Period to Trial Day 30 Visit in MADRS total score • Change from Study Part B Baseline to Re-Administration Day 30 Visit in MADRS total score
Characterize the PERSISTING (~30 days post-dose) effects of PAT at two possible administrations on psychological flexibility measured via the MPFI	• Change from Study Part A Screening/Baseline Period to Trial Day 30 Visit in MPFI score • Change from Study Part B Baseline to Re-Administration Day 30 Visit in MPFI score

OBJECTIVES	ENDPOINTS
Exploratory	
Characterize participants' subjective experience of PAT in the context of a clinical trial with the EMPATHY semi-structured qualitative interview	• Qualitative changes in responses between Screening/Baseline Period Entrance Interview and Exit Interviews after Trial Day 30 Visit or Re-Administration Day 30 Visit
Assess acceptability, appropriateness and feasibility of implementing PAT from the participant and researcher perspectives using AIM, IAM and FIM[65] at two possible administrations	• Evaluated at Study Part A Trial Day 30 Visit and Re-Administration Day 30 Visit, when applicable
Characterize IMMEDIATE (during psilocybin dosing) and ACUTE (~1-week post-dose) effects of PAT in depressed adults at two possible administrations on: • Neural structure and functioning (structural, blood flow, extended resting state fMRI); • Proteomic blood biomarkers (SASP profile)	• Change from Study Part A Baseline to Trial Day 8 Visit: • Whole brain FC • FC within and between brain networks involved in TRD [DMN, SN and central executive network (CEN)] • SASP blood biomarkers of cell senescence and inflammation • Change from Study Part B Baseline to Re-Administration Day 8 Visit: • Whole brain FC • FC within and between brain networks involved in TRD [DMN, SN and central executive network (CEN)] • SASP blood biomarkers of cell senescence and inflammation
Characterize PERSISTING (~30 days post-dose) effects of PAT in depressed adults at two possible administrations on: • Neural structure and functioning (structural, blood flow, extended resting state fMRI); • Proteomic blood biomarkers (SASP profile)	• Change from Study Part A Baseline to Trial Day 30 Visit: • Whole brain FC • FC within and between brain networks involved in TRD [DMN, SN and CEN] • SASP blood biomarkers of cell senescence and inflammation • Change from Study Part B Baseline to Re-Administration Day 30 Visit: • Whole brain FC • FC within and between brain networks involved in TRD [DMN, SN and CEN] • SASP blood biomarkers of cell senescence and inflammation
Characterize PERSISTING (~30 days post-dose) effects of PAT in depressed adults at two possible administrations on cognitive functioning via the NIH Toolbox Cognitive Function Battery (NIHT-CFB) tests of Executive Functioning, Working Memory, and Processing Speed	• Change in scores from Study Part A Screening/Baseline Period to Trial Day 30 Visit • Change in scores from Study Part B Baseline to Re-Administration Day 30 Visit

4 STUDY DESIGN

4.1 OVERALL DESIGN

This Phase 2b open-label pilot study will evaluate the feasibility of conducting neuroimaging and collecting blood biomarkers on depressed adults through a PAT protocol and characterize changes in ACUTE and PERSISTING effects of PAT. Eligibility will be based upon DSM-5 criteria using the MADRS and a Structured Clinical Interview (SCID-5-CT).

Up to 50 eligible depressed, otherwise healthy adult participants (≥18 years old) will be enrolled. In Study Part A participants will undergo one open-label psilocybin (25mg) dosing administration along with psychological support before, during, and after the dosing session. When feasible, participants will undergo neuroimaging and the collection of blood biomarkers with the purpose of characterizing the effects of age-related biomarkers of depression and response to treatment with PAT. At the end of Trial Day 30, participants will be evaluated for eligibility to receive a re-administration of psilocybin (25mg) along with psychological support in Study Part B.

Part A of the study consists of 3 periods: a Screening/Baseline Period of approximately 28 days, followed by a Dosing Day, and a Follow-up Period of approximately 30 days (See **Error! Reference source not found.**). Eligible participants will enter the Part B Re-administration period (See

Table 1.2: PART B - Re-Administration Schedule of Activities (SOA#2)) which will up to approximately an additional 6 weeks.

Study Activities

Blood Biomarkers

Participants may have blood drawn for proteomic analysis at approximately 6 study visits during Study Part A and 5 study visits during Study Part B. On dosing day, participants may have blood drawn approximately between one and six hours before receiving the medication. Approximately 30 ml (approximately 2 tablespoons) of blood will be drawn at each assessment time point, totaling 240 ml from each participant during study participation. Individuals who choose to continue to Study Part B will provide an additional 30 ml of blood per assessment timepoint, totaling 210 ml of blood.

Brain Imaging

Participants may undergo brain imaging at up to 10 separate sessions. When feasible, participants will undergo 2 MRI scans during the Screening/Baseline Period, 1 MRI scan on dosing day, 2 scans within 7 days post dosing session, 2 scans around Day 15, and 2 scans around Day 30 with the goal of obtaining at least 30 minutes of useable scanning data at each time point. Participants who enter the re-administration period may undergo an additional 10 scanning sessions. The number of time points acquired may vary based upon scanner and participant availability, and scanner support. See "MRI Sequences" below for further details.

Psychological Support

Participants will receive psychological support for their psilocybin administration session based upon the Phase 3 clinical trial of psilocybin-assisted therapy for depression conducted by the Usona Institute (Appendix B).[66] Participants are paired with 2 Study Facilitators who provide a supportive context for the psilocybin administration session, including preparation before and integration after drug administration. The assigned Lead Facilitator will remain with the participant throughout all preparation, dosing and integration sessions. The Assistant Facilitator will attend at least 1 preparation session, the dosing session, and may attend integration sessions. Study Facilitators are also trained to identify, document and notify the study clinician, when necessary, of any adverse events study participants may experience throughout their psilocybin administration session.

Lead Facilitators have graduate-level training and clinical experience in psychotherapy. Assistant Facilitators hold a minimum of a bachelor's degree and at least 1 year of experience in a mental healthcare setting. Both Lead and Assistant Facilitators will have adequate training to identify safety issues during the participant's preparation, dosing, and integration sessions. For this protocol, we will reference applicable training from the Usona Institute Clinical Facilitator Manual (Appendix C). For training purposes and to monitor fidelity to the therapeutic protocol, sessions with the Facilitators may be audio and/or video recorded.

Preparation Sessions

Participants will complete 2 preparatory sessions lasting approximately 8 hours up to two weeks prior to the dosing session with their assigned Facilitators. Preparation for a psilocybin session is critical to establish a therapeutic "set," and to minimize the likelihood of adverse psychiatric reactions. Preparation sessions serve as an opportunity for participants and Facilitators to build rapport and for Facilitators to educate

participants about the upcoming psilocybin administration.[64] Part of the preparation will be discussing the procedures for brain imaging and blood draws on dosing day.

Preparation sessions allow Facilitators to develop an understanding of the participant's life history, lived experience with depression, and intentions and expectations of the dosing session. These sessions also help Facilitators identify areas that impact the dosing experience and identify any warning signs that the participant may not be psychologically safe or eligible for the dosing session. Whenever possible, preparation sessions will occur in the dosing room so participants can develop a level of comfort and familiarity with the intervention location.

Facilitators will refer to and complete the Facilitator Approach Checklist and Facilitator Preparation Checklist during the preparation sessions as found in the USONA Clinical Facilitator Manual (Appendix C).

For Re-administration, preparation sessions will last approximately 90 minutes, and will be done in person, when possible.

Additional details about content and structure of preparation sessions are described in the Schedule of Activities (**Error! Reference source not found.** and

Table 1.2) and in the USONA Clinical Facilitator Manual (Appendix C).

Dosing Session

The study participant will be supported throughout the dosing session by two study Facilitators. Facilitators will continuously observe and evaluate the participant's physical and mental status to provide reassurance and emotional support should the participant experience strong emotions or become anxious or agitated during the session. Facilitator teams are minimally directive, neither guiding the participant nor routinely making therapeutic interventions, instead facilitating the subject's own inner experience, and providing psychological and emotional support when it is wanted or needed. Participants are asked to follow wherever the experience leads.

Integration Sessions

Participants will complete 3 integration sessions (scheduled at approximately Trial Days 2, 8, and 15) which are expected to last approximately up to 4 hours (80 minutes each) with one or both Facilitators. Integration sessions are conducted in-person and include a psychological support-focused discussion on the dosing experience, integration process, and instructions for after-care. Integration sessions are participant led and are intended to help the participant integrate and process the experience, and to assess and manage any adverse events that may emerge. During integration, participants may reflect, discuss, and identify thoughts and feelings about the material that emerged during the dosing session, and Facilitators offer guidance on how to integrate insights from the dosing session into the everyday life of the participant. Facilitators will use "Facilitator Integration Checklist" as found in the USONA Clinical Facilitator Manual (Appendix C) to guide each integration session. More details on the contents and structure of the Integration Sessions can be found in the Usona Clinical Facilitator Manual (Appendix C).

EMPATHY Interview

The Explanatory Models in Psychedelic-Assisted Therapy (EMPATHY) 20-item semi-structured qualitative interview was developed by our research team based on the Kleinman explanatory model of illness (Appendix D).[67, 68] EMI is a framework in medical anthropology for understanding how patients' cultural beliefs shape their perception, experience, and response to illness, focusing on their ideas about causes, onset, severity, effects, and desired treatments, contrasting with the clinician's biomedical view to improve cross-cultural communication and care. The EMPATHY Interview will be conducted at baseline and at completion of study participation.

Study Periods

Screening/Baseline Period (Can last up to approximately 28 days prior to Dosing)

After passing an initial phone pre-screening, potential participants will be scheduled for a Screening Visit. The Informed Consent Form (ICF) must be signed prior to starting any study-related assessments at the Screening Visit. The Screening/Baseline Period begins when a participant signs the written ICF.

During the Screening/Baseline Period, participants will complete additional interviews, safety assessments and clinical assessments. When feasible, participants will also undergo baseline MRI scans. Participants will complete two preparatory sessions lasting approximately 8 hours conducted by the session Facilitators prior to dosing.

The Screening Visit may require multiple days/visits to reduce participant burden and allow for appropriate assessment. The purpose of the Screening Visit(s) is to evaluate medical and psychiatric appropriateness for the study. Enrolled participants will receive a panel of screening safety labs, an electrocardiogram, a health and physical exam, and will complete psychiatric assessments and an MRI safety screening form. A complete listing of Screening Activities is listed in SOA#1 (**Error! Reference source not found.**).

Participant eligibility will be determined during the Screening Visit and will be continually evaluated at each study visit. If at any point the participant is found ineligible, the study visit may be discontinued, and any remaining procedures will not take place.

Dosing Session (Day 1)

Dosing with the study drug will occur after all pre-dose assessments are completed and continued eligibility is determined. Participants will receive a single oral dose of psilocybin 25mg administered as a capsule taken with approximately 8 ounces of water. Dosing will occur in the HML at the WUSM campus, in a dedicated space equipped with a bed, lighting, chairs and audio equipment specifically for psilocybin studies.

To reduce distractions and interruptions, only the participant and the Facilitators will be in the study room once the study drug has been administered. Both Facilitators will be present in the dosing room throughout the entire dosing session to ensure the participant receives reassurance and emotional support should they become anxious or agitated during the session. Facilitators will monitor the participant for physical and emotional safety throughout the session and will consult the study clinician if immediate clinical assessment is needed. Facilitators will document the participant's vitals (HR and BP) and any adverse events throughout the dosing session using the Dosing Day Monitoring Form as found in the USONA Clinical Facilitator Manual (Appendix C**Error! Reference source not found.**) and Dosing Day Vitals Guidance (Appendix E). Facilitators may take short breaks for meals or to use the restroom. At least 1 Facilitator will always be present in the dosing session room. A study clinician will be on-call throughout the duration of the dosing session and will be available to be on-site within approximately 15 minutes in the event of an emergency for medical/psychiatric assessment. The study clinician is responsible for administering rescue medications, should these be warranted.

After taking the study drug, participants will lie supine with eyeshades on and listen to a pre-selected playlist of standardized music through headphones. Participants will be encouraged to turn their attention inward as they focus on what arises in the present, without judging the experience as good or bad.

When feasible, participants will undergo brain imaging during the dosing session. After taking the study drug, participants will be encouraged to wear the eyeshades and headphones while being transported to the MRI scanner. Facilitators will accompany participants to the neuroimaging session and will stay with the participant throughout the imaging process. Following the completion of imaging, participants will return to the dedicated dosing room in the HML.

The acute effects of psilocybin typically last 4.5-7 hours. Facilitators will begin to evaluate participants for release 7-hours post-dosing using the following criteria:

- Vital signs: BP and HR are acceptable.
- Participant is alert and oriented to person, place, and time.
- Participant has indicated peak subjective effects have subsided.
- Participant does not self-report or exhibit signs of confusion, anxiety, paranoia, delusions, suicidality, or psychotic symptoms.

- Participant has indicated that they feel safe and competent to leave.
- Participant is not showing any symptoms or signs that would pose a risk for discharge.

If the participant appears to have met the above criteria, the Lead Facilitator and the study clinician will evaluate the participant's readiness to be discharged using the Participant Release Checklist as found in the USONA Clinical Facilitator Manual (Appendix C). Participants will complete study assessments as listed in SOA#1 or SOA#2 prior to discharge. Participants will be released to the care of their support person and will be instructed not to drive until the next day. The study clinician and Lead Facilitator will be on-call following participant release until the following morning when the participant returns for the Trial Day 2 Visit should any issues or safety concerns arise.

Participants experiencing residual IP effects, such as mild persistent sensorial distortions, will be asked to remain on-site for continued observation by Facilitators and/or the study clinician until cleared to leave with the support person. Participants who are experiencing severe physical or perceptual drug effects or are exhibiting signs of significant/severe emotional distress including suicidal ideation will be evaluated by the study clinician for transport to the emergency department for further assessment. Rescue medications are described in Section 6.5.3 and may be used at the discretion of the study clinician.

Follow-Up Period (Trial Day 2- Trial Day 30)

During the Follow-up Period, participants will complete additional interviews, safety assessments and clinical assessments. When feasible, participants will undergo MRI scans at approximately 7 days and 14 days post-dosing. During this period, participants will participate in 3 integration sessions with the Study Facilitators.

At the Trial Day 30 Visit, safety assessments, lab assessments and psychiatric assessments will be completed per SOA #1 (**Error! Reference source not found.**). Participants who are eligible for re-administration move into the re-administration period, SOA #2 (

Table 1.2).

Re-administration Period

After the completion of the Trial Day 30 assessments, participants who meet the re-administration criteria will be offered an open-label trial of psilocybin 25mg. Participants will follow SOA #2 (

Table 1.2).

Prior to re-administration, participants will have one re-administration preparation session with the study Facilitators lasting approximately 90 minutes. After re-administration dosing day, participants will have 3 integration sessions with the study Facilitators following the same format as during the first dosing session.

4.1.1 MEASURES TAKEN TO MINIMIZE BIAS

Measures will be taken to minimize bias, including the use of qualified and trained raters for the primary outcome measures.

To assess the role of expectancy in treatment response, the Credibility and Expectancy Questionnaire will be administered to participants at various points during Study Part A and Study Part B, as indicated in the Schedule of Activities (Section 1.3).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Here, we propose a mechanistic study of the effects of PAT as augmentation to traditional antidepressant treatment (e.g., selective serotonin and norepinephrine reuptake inhibitors or SSRIs and SNRIs, or atypical antidepressants (bupropion or mirtazapine) in persisting depression.

The neural and molecular mechanisms of treatment response in MDD are poorly understood. Studies focusing on functional neuroimaging analysis have shown that MDD is consistently associated with reduced FC within the DMN, hyperactivity in individual DMN regions, and decreased FC between the DMN and other brain regions.[69] A recent meta-analysis also demonstrated that a high burden of cerebrovascular disease is strongly associated with lower remission rates of depression in older adults.[70] Despite their relevance, neuroimaging studies are limited since they do not identify the underlying molecular mechanisms of treatment resistance that can be targeted for interventions. The precision functional mapping approach measures brain connectivity changes in single participants by comparing multiple imaging time-points in each study condition. When feasible, participants will undergo up to 10 brain imaging sessions in Part A of the study. Additionally, participants who are eligible for re-treatment will undergo up to an additional 10 brain imaging sessions in Part B of the study. By acquiring large amounts of data on a small number of participants, we can substantially increase effect size and statistical power by removing the variance associated with averaging brain imaging data across humans. The number of time-points acquired may vary based on availability of scanner time, participants, and scanner support.

We are exploring SASP proteins as potential prognostic and mechanistic markers of cellular senescence, which accumulates and lead to aging-related pathology. The SASP proteins reflect interrelated biological processes, and examining them as a biomarker composite index (SASP index) may be a particularly robust marker for assessing cellular senescence and its response to therapeutics.[22] While the SASP is cell-dependent, there are common SASP proteins expressed by senescent cells. Our group developed a peripheral SASP index comprised of 22 proteins. We validated the SASP index and found it was increased in older adults with depression. This elevation was most marked in TRD[22] and higher SASP levels were associated with greater levels of comorbid physical health conditions and cognitive impairment.[71]

Justification for Dose

For a detailed review of non-clinical pharmacology, clinical trial results, adverse events and pharmacokinetics, see Usona Investigator's Brochure (Appendix A). Briefly, the 25 mg oral psilocybin dose is being used in Phase II and III clinical trials for depression because dose-finding studies and historical weight-based data identified it as a high, effective therapeutic dose that consistently produces a robust psychedelic experience thought to be crucial for sustained antidepressant effects, while maintaining a favorable safety and tolerability profile. Clinical trials have demonstrated that a 25 mg dose has a

substantially larger and clinically significant antidepressant effect compared to lower doses, such as 1 mg or 10 mg. Lower doses did not produce a significant clinical response in some studies, establishing 25 mg as a more effective benchmark.[2, 4] Early trials often used weight-adjusted doses (typically 0.2-0.4 mg/kg of psilocybin per session). A fixed 25 mg dose is consistent with this earlier research (approximately 0.3 mg/kg for a 70 kg person) and has been validated in secondary analyses as producing comparable psychedelic effects to the weight-based approach.[72] Psilocybin's primary mechanism of action involves acting as an agonist for the serotonin 5-HT2A receptors.[73] This activation is linked to enhanced neural plasticity, reorganization of brain networks (particularly the DMN), and the profound altered states of consciousness (the "psychedelic experience") hypothesized to facilitate therapeutic breakthroughs and long-lasting psychological changes. The 25 mg dose is considered a high therapeutic dose capable of reliably inducing these robust effects. Studies have indicated that psilocybin at doses of 10 mg or 25 mg is safe and generally well-tolerated in controlled clinical settings with psychological support. While transient adverse events such as headaches, nausea, or anxiety may occur, no serious drug-related adverse events have been reported in these controlled trials. The 25 mg dose is considered to balance the need for a potent therapeutic effect with manageable side effects,[74] with evidence that this dose is well-tolerated in individuals treated with an adequate dose of a serotonergic antidepressant. The 25 mg dose has been associated with rapid and sustained antidepressant effects lasting several weeks to months after a single administration when combined with psychological support, suggesting a durable clinical benefit.[5] In summary, the selection of the 25 mg dose is a data-driven decision, balancing maximum clinical efficacy with patient safety and consistent results across various trials.

End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SOA #1 and #2), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SOA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Age ≥ 18 years
2. Participants of childbearing potential must agree to practice 2 forms of effective birth control throughout the duration of the study (Appendix F)
3. Females of childbearing potential must have a negative urine pregnancy test at Screening and prior to dosing on Dosing Day
4. Diagnosis of depression at Screening via the SCID-5-CT interview and MADRS score of ≥7
5. Have an identified support person
    - *Agree to be accompanied home (or to an otherwise safe destination) by the support person, or another responsible party, following dosing*

5.2 EXCLUSION CRITERIA

If a participant meets any of the exclusion criteria listed below at any point prior to dosing, they will be excluded from the trial and cannot proceed further:

1. Unable to read or understand English
2. Is currently pregnant or breastfeeding, or plan to become pregnant or breastfeed within the study period

3. Has had Electroconvulsive Therapy, Transmagnetic Stimulation, Vagus Nerve Stimulation or Deep Brain Stimulation treatment within the last 12 months
    a. *Participants with VNS or DBS devices in place- including devices that are inactive or turned off will not be eligible to participate in the imaging portion of the study*
4. Is currently taking a medication on the prohibited medications list (Appendix G), such as heterocyclic (tricyclic, tetracyclic) antidepressants, monoamine oxidase inhibitors (MAOIs), antipsychotic augmentation therapy, or is taking more than one medication for the treatment of depression:
    a. *Participants who are taking a single prescription medication for depression must be on a stable, minimally therapeutic/tolerated dose for at least 4 weeks prior to Screening. (Appendix H)*
    b. *Psychostimulants for the treatment of attention-deficit/hyperactivity disorder (ADHD) are allowed, if used at a stable dose or pattern for at least 6-weeks prior to Screening and not used on Dosing Day(s).*
5. Has a primary psychotic disorder diagnosis
6. Has a first-degree relative with a known history of a psychotic disorder
7. Meets criteria for substance use disorder or diagnosis of substance use disorder within 6 months prior to Screening
8. Has an unstable medical condition or serious abnormalities of complete blood count, chemistries, or ECG, or taking medications that in the opinion of the study clinician would preclude safe participation in the trial
9. Is at risk for hypertensive crisis defined as:
    a. *BP at Screening AND Baseline >140/90 mmHG*
    b. *BP on Dosing Day prior to dosing >140/90 mmHG*
10. Has used a serotonergic hallucinogenic substance (e.g., psilocybin, lysergic acid diethylamide (LSD), mescaline, N,N-dimethyltryptamine (DMT), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), ibogaine, 3,4-methylenedioxymethamphetamine (MDMA), or other related substances) within 6 months of Screening.
11. Has a known sensitivity to psychedelic medications
12. Has a positive urine drug test including amphetamines, barbiturates, buprenorphine, benzodiazepines, cocaine, methamphetamine (unless prescribed), MDMA, methadone, opiates, and phencyclidine (PCP)
13. Is at high risk for suicide (e.g., active suicidal ideation and or current intent or plan) and unable to be managed safely (i.e., unwilling to be hospitalized)

5.3 CRITERIA FOR PSILOCYBIN RE-ADMINISTRATION

Participants who continue to have depressive symptoms (MADRS score ≥ 7) and who continue to meet inclusion/exclusion criteria at end of the initial dosing period may be eligible for 1 re-administration of psilocybin 25mg.

5.4 LIFESTYLE CONSIDERATIONS

The following lifestyle restrictions apply during participation in this trial:

- Fasting: Participants should fast for ≥3 hours prior to trial intervention dosing. Drinking water is permitted.
- Psychoactive Substances: Participants should avoid using psychoactive substances (i.e. caffeine, alcohol, nicotine, cannabis) within 8 hours before the start of any study visit that includes imaging or dosing.
- Driving: Participants must agree to be driven home following dosing with psilocybin.

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study.

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will occur at a single site and will screen participants until target enrollment of 50 participants is reached. A screen-fail rate of 50% is anticipated.

Participants will be recruited via the electronic health record, through word of mouth and referrals by colleagues. Participants may be recruited through the HML website (*www.healthyminds.wustl.edu*), CHIRP website (*https://sites.wustl.edu/centerforpsychedelics/*), flyers, and email notification. Participants will be considered eligible per the inclusion/exclusion criteria and at the PI's determination, will be able to tolerate all study procedures and medications, and able to give informed consent. Adults 18 and older will be enrolled without regard to gender, race, ethnicity, or religion. Potential participants undergo screens first by phone and then an in-person visit that includes a psychiatric and medical history, blood chemistries, and an ECG.

A modest financial compensation is provided for time. This includes $100 for in-person study visits and $250 each dosing day. However, participation is expected to be motivated, in large part, by a desire to contribute to an understanding of psilocybin's effects on the brain. Participation in the proposed study-supported activities will be entirely voluntary and permitted only following completion of all consent-related procedures. We view informed consent as an ongoing process and will continue the informed consent conversation with participants throughout their participation in this study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Information about the IP is provided in Table 6.1.

Table 6.1: Details of Investigational Product

Trade Name	Psilocybin
Manufacturer	Almac/Lonza[a]
Doses	25 mg (capsule)
Route of Administration	Oral
Formulation	Capsule
Strengths	25 mg

[a]Our partner and drug supplier, Usona Institute has developed psilocybin for oral administration (25 mg, single dose) in conjunction with a supportive set and setting protocol for MDD. Usona Institute is a non-profit medical research organization founded in 2014 that conducts and supports biochemical and clinical research to further the understanding of the therapeutic effects of psilocybin and other consciousness-expanding medicines. Additional information about Usona can be found at www.usonainstitute.org.

Refer to the current version of the psilocybin IB for a detailed description of the IP (Appendix A).

Psilocybin has not been approved as a treatment for any condition by government agencies in any country, except for Australia where psilocybin can be prescribed by specifically authorized psychiatrists for the treatment of TRD.[75] The safety and effectiveness of psilocybin is still being studied.

6.1.2 DOSING AND ADMINISTRATION

Drug administration will take place in the HML at the WUSM campus, in a dedicated neuropsychological testing room modified specifically for this study. Prior to dosing, participants will have a final eligibility check by the study team including collection of vitals, a urine pregnancy test and a urine drug screen. Participants will be asked to fast for at least 3 hours prior to dosing.

Upon confirmation of eligibility, the participant will receive a single dose of the study drug (25mg psilocybin) taken with approximately 8 ounces of water under the supervision of study facilitators while in the dosing room.

After drug administration, participants will be transported to the MRI lab for MRI scanning.

Following completion of imaging, participants will return to the HML. The participant will be encouraged to relax, wear eye shades and headphones with pre-selected music, and to direct their attention to the internal experience for the rest of the day. The participant will remain in the session room except to use the bathroom. The participant will receive psychological support from the trained Facilitators throughout the day. At least one Facilitator will be with the participant at all times. Facilitators will monitor the participant for adverse events and will record vitals throughout the day. A clinician will be on-call should any serious adverse event occur. Participants will be evaluated for release starting at 7 hours post dose by the Facilitators and the study clinician using the Participant Release Evaluation found in the USONA Clinical Facilitator Manual (Appendix C). The participant will be released to the care of their identified support person. Participants will be instructed to not drive until the next day.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Psilocybin study medication will be ordered and supplied by Usona Institute in 25 mg oral capsules through a contract with Usona Institute (via Almac Clinical Services who provide study drug in secure packaging for clinical research studies) who have also provided support to this extended access IND application with a LOA to allow us to cross reference their IND 129532. `

6.2.1.1 RECORD KEEPING

WUSM will maintain documentation to clearly record their process for investigational product receipt and dispensation.

Documentation will consist of:

- DEA 222 Forms will be used to document ordering and receipt of investigational product; these forms will remain on site and stored separately from other trial documents.
- The Delegation of Authority Log will identify staff authorized to dispense and administer IP.
- The Investigational Product Accountability Log will be completed upon each dispensation and administration of IP to maintain the count of IP on site from the time the IP is received, after each administration, until completion of the trial.
- Investigational product administration will be documented per occurrence noting which study participant received IP and which staff member administered IP.
- The Schedule I license holder will periodically perform IP accountability review or instruct the pharmacy staff to do so on their behalf to ensure proper dispensation documentation on the Investigational Product Accountability Log.

All records will be kept for at least six years. The name of the individual on the DEA application for registration (Dr. Ginger Nicol) is the only individual that can order controlled substances and sign for the controlled substances when they are received. If a Power of Attorney would be utilized, a copy of the Power of Attorney would be provided.

6.2.1.2 RECEIPT OF INVESTIGATIONAL PRODUCT

For the duration of the study, all IP received shall be considered a Schedule I controlled substance, unless the study drug is re-classified. Records shall be maintained documenting the date the shipment was received. With each shipment, the investigational product shall be verified against the packing list upon receipt and confirmed within the electronic study database. Any damaged or otherwise unacceptable investigational product shall be documented and quarantined.

Once the investigational product is received in Dr. Nicol's office, the product will be counted in the presence of a second individual to confirm accuracy, and the packing slip will be signed and dated by the person receiving (opening) the package. The quantity and date received will be recorded along with the printed names and signatures of the person receiving the IP and the witness.

6.2.1.3 DISPENSATION OF INVESTIGATIONAL PRODUCT

Only authorized study staff may dispense or administer investigational product. Such authorized staff shall be documented on the Delegation of Authority Log. Each administration of investigational product shall be documented on Investigational Product Accountability Log and recorded in the electronic study database.

6.2.1.4 INVESTIGATIONAL PRODUCT DESTRUCTION

Upon completion of the trial, any remaining investigational product at WUSM shall be destroyed using a DEA-licensed reverse distributor, or by other appropriate means. Should any controlled substance become unusable, tainted, or exceed the expiration date, we will follow institutional procedures for Controlled Substances Obtained with Individual Research Registrations. Drug will be transferred to the Barnes Jewish Christian (BJC) Hospital (the primary hospital system affiliated with WUSM) pharmacy for disposal and the transfer documented according to institutional procedures. A DEA FORM-41 will be mailed to the local DEA office prior to destruction.

6.2.1.5 LOSS OR THEFT OF INVESTIGATIONAL PRODUCT

In the event of loss or theft, DEA FORM-106 will be submitted as soon as possible, and the local DEA and/or State Police Department and the controlling board for the state of MO will be notified. The controlled substance will be kept in a locked room and always secured with a key lock when not being dispensed. Only the individuals referenced in #9 will have access to this room. Our building is additionally equipped with security cameras and electronic locks requiring a pin/badge number to enter and security services are provided by BJC and WUSM. An inventory of all IP kept within the locked room will be conducted each time drug is dispensed as well as periodically, but no less than monthly.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

6.2.2.1 FORMULATION

Psilocybin ([3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate) is a tryptamine derivative presenting as a white crystalline solid with a melting point of 220-228°C. It is stable over extended periods in dark storage at controlled room temperature. Psilocybin is soluble in 20 parts boiling water or 120 parts boiling methanol.

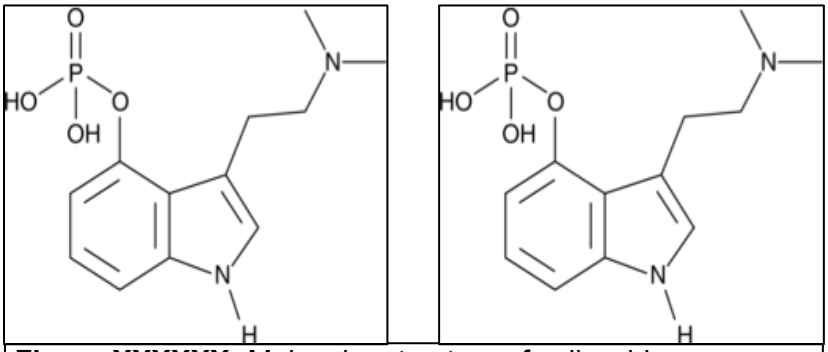


Figure XXXXXX: Molecular structure of psilocybin.

6.2.2.2 APPEARANCE

Psilocybin is provided as 25 mg capsules (size 2, hydroxypropyl methyl cellulose, white).

6.2.2.3 PACKAGING

Psilocybin capsules are packaged individually into high-density polyethylene bottles.

6.2.2.4 LABELING

Psilocybin bottles will be labeled with appropriate bottle numbers.

The IP will be packaged and labeled by Almac/Lonza in accordance with applicable national laws.

6.2.3 PRODUCT STORAGE AND STABILITY

IP will be stored in accordance with the Missouri State Code of Regulations (CDR), Division 30 Regulation and Licensure and Controlled Substance Reporting. We will also follow Missouri state guidelines on reporting loss or diversion of IP.

IP will be stored at the HML, Department of Psychiatry, WUSM, Taylor Avenue Building, Suite 121. The 7,000 square foot research location is equipped with security cameras and all doors to enter the building and research lab require a pin or badge to open an electronic lock.

IP will be stored in a substantially constructed metal cabinet equipped with a key dual lock in Room 123F, a temperature-controlled plaster/steel and drywall room with a solid wooden door that is also equipped with a key lock. Access to the drug storage room will be limited to Dr. Ginger Nicol, Dr. Eric Lenze, Julie Schweiger, and Angela Stevens. The door will always remain locked when not occupied. The controlled substance will not leave the room until it is dispensed.

All staff working on the study will be certified through CITI and GCP training. Should any controlled substance become unusable, tainted, or exceed an expiration date, the drug will be disposed of according to institutional and DEA procedures and proper documentation will be completed and retained.

Campus security provided by BJC and WUSM patrols all buildings on campus.

Contact information for WUSM campus security:

Washington University Campus Police
6615 Shepley Dr., Clayton, MO 63105
314-935-5555
314-362-4357

6.2.4 PREPARATION

Capsules will be administered orally with 8 oz of water. Capsules will not be opened or chewed.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 RANDOMIZATION

Randomization does not apply to this trial.

6.3.2 BLINDING

Blinding does not apply to this trial.

6.3.3 UNBLINDING

Unblinding does not apply to this trial.

6.4 STUDY INTERVENTION COMPLIANCE

The study drug will be administered under the study team supervision. Compliance with intervention procedures will be documented and recorded in the CRF.

6.5 CONCOMITANT THERAPY

Participants will continue their previous anti-depressant monotherapy.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and supplements. All prescription and non-prescription medications (e.g., over-the-counter medications and herbal supplements) that participants report taking during the 30 calendar days prior to Screening and during the Screening/Baseline, will be recorded in the CRF as prior medications.

All changes, additions, or discontinuations to medications will be assessed and recorded in the CRF during each trial visit.

6.5.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

The following medications and therapies are prohibited starting from Screening/Baseline until the final Follow-up visit:

- MAOI antidepressants (e.g., isocarboxazid; phenelzine; seligiline; tranylcypromine)
- Heterocyclic (tricyclic and tetracyclic) antidepressants (e.g., amitriptyline; amoxapine; clomipramine; desipramine; doxepin; imipramine; maprotiline; nortriptyline; protriptyline; trimipramine).
- Typical, or First Generation, antipsychotics (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine).
- Atypical, or Second Generation, antipsychotics (aripiprazole, asenapine, cariprazine, clozapine, iloperidone, lumateperone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone).
- Alternative or complimentary antidepressant augmentation agents with serotonergic activity, such as S-adenosylmethionine or St John’s Wort, etc.

- Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (TMS), Vagal Nerve Stimulation (VNS), or Deep Brain Stimulation (DBS) in the past year.
- Known UDP or UGT enzyme modulators (e.g., atazanavir, diclofenac [topical formulations allowed], mycophenolic acid, quinidine, ritonavir, silybin, valproate/valproic acid, or phenobarbital).
- Known alkaline phosphatase inhibitors (e.g., levamisole, theophylline).
- Efavirenz (an antiviral that can cause hallucinations)
- Psychedelic substances, including psilocybin (excluding psilocybin administered as IP), LSD, mescaline, DMT, 5-MeO-DMT, ibogaine, MDMA, or other related substances with known psychedelic effects that act on the 5HT2A receptor.
- Nicotine on IP dosing days during the dosing period (approximately 8 hours).

Further details about prohibited medications are provided in Appendix G.

6.5.2 PERMITTED CONCOMITANT MEDICATIONS

The following medications and therapies are permitted starting from Screening (after the ICF is signed) until the final Follow-up visit:

- Stable dose benzodiazepines, non-benzodiazepines (e.g., zolpidem, zaleplon, and eszopiclone), or orexin antagonists for the treatment of insomnia.
- Benzodiazepines are permitted on Dosing Day as rescue therapy.
- Stable dose psychostimulants for the treatment of ADHD or weight loss. Psychostimulants may not be taken on IP dosing days.
- Prescribed opiates (e.g., methadone, buprenorphine, oxycodone, etc.) are permitted if limited to a brief course (i.e., ≤3 days) completed at least 1 week prior to Dosing Day or Re-administration Baseline.

6.5.3 RESCUE MEDICINE

In the unlikely event that a participant requires medication management for adverse physiological (i.e., BP, HR) or adverse psychological (i.e., anxiety, psychosis) symptoms, the study clinician may use the following medications (or similar medications available locally) per their medical discretion:

1. Nitroglycerin: hypertension
2. Clonidine: hypertension
3. Lorazepam: anxiety, agitation
4. Risperidone: anxiety, agitation, psychosis
5. Ondansetron: nausea, vomiting

The use of rescue medications to control symptoms will be at the judgment of the study clinician. The date and time of medication administration, reason for administration, as well as the name and dosage regimen of the rescue medication will be recorded on a Concomitant Medications log. Use of psychotropic agents (e.g., lorazepam, risperidone) will be on a 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 clinician will determine if the participant can be safely escorted by medical staff to an emergency room (located on the same campus as the medication dosing room or the nearest emergency department), or if 911 needs to be called for transport. Other medical care will be provided at the discretion of a licensed clinician.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Participants are free to withdraw from participation in the trial at any time upon request. The trial may also be terminated due to any of the reasons in Section 7.2.

Given that each dosing day includes only a single dose of study drug, there are no halting rules. If a clinically significant finding is identified (including but not limited to changes from baseline) after enrollment, the Principal Investigator will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

If a participant is discontinued at any time after enrollment into the trial for any reason, the Investigator will make every effort to follow the participant and complete the Trial Day 30 Visit assessments as shown in SOA#1 (**Error! Reference source not found.**).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

If a participant withdraws consent for disclosure of future information, the Principal Investigator/Sponsor may retain and continue to use any data collected before withdrawal of consent. Additionally, if a participant withdraws from the trial, they may request destruction of any stored/unanalyzed biological samples, and the Principal Investigator must document this in the study records.

The reason for participant discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (eCRF) from one of the following standard categories:

- Withdrawal of Consent: The participant desired to withdraw from further participation in the trial. If the participant gave a reason for withdrawing, it should be recorded in the termination form.
- Adverse Event: Clinical or laboratory events occurred that, in the medical judgment of the Investigator for the best interest of the participant, are grounds for discontinuation. These events include SAEs and nonserious AEs regardless of relation to the trial intervention.
- Protocol Deviation: The participant's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements.
- Lost to Follow-up: The participant stopped coming for visits and trial personnel were unable to contact the participant.
- Death: The participant died.
- Other: The participant was discontinued for a reason other than those listed above, such as theft, loss of trial intervention, or termination of the trial.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to complete at least one study visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return for a required study visit:

- The site will 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 if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will 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 medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING ASSESSMENTS

8.1.1 CONTACT FORM

The Contact Form is completed during the phone screen to collect contact information about the participant (e.g., full name, phone, email, mailing address and emergency contact information).

8.1.2 DEMOGRAPHICS QUESTIONNAIRE

The Demographic Questionnaire obtains information on age, gender, race, ethnicity, level of education, employment status, etc.

8.1.3 MEDICATION HISTORY QUESTIONNAIRE

A detailed medical history of the participant will be taken including a list of current prescribed, over the counter and supplemental medications, the medicine's indications and length of time on each medication at screening.

8.1.4 PATIENT HEALTH QUESTIONNAIRE-9

The Patient Health Questionnaire-9 (PHQ-9) is a self-report instrument used to screen, diagnose, monitor, and measure the severity of depressive symptoms.[77]

8.1.5 PSYCHOSIS SCREENING QUESTIONNAIRE

The Psychosis Screening Questionnaire (PSQ) is a brief semi-structured interview used to identify participants at high-risk for developing psychotic symptoms during drug exposure.[78]

8.1.6 MEDICAL HISTORY QUESTIONNAIRE

The HML Medical History Questionnaire will gather information about the participant's medical history.

8.1.7 STRUCTURED INTERVIEW FOR DSM-5 DISORDERS-CLINICAL TRIALS VERSION

The Structured Clinical Interview for DSM-5 Clinical Trials (SCID-5-CT) is a specialized version of the SCID-5 designed for use in clinical trials to ensure accurate diagnosis and assessment of mental health disorders.[79]

8.1.8 MASSACHUSETTS GENERAL HOSPITAL ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) is a standard validated measure for assessing antidepressant treatment history.[80] The geriatric version of the ATRQ will be administered to participants who are ≥65 years of age.

8.2 EFFICACY ASSESSMENTS

The following assessments will be performed throughout the trial as noted in the SOAs (Section 1.3).

8.2.1 MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE (MADRS)

The MADRS is clinician-administered 10-item depression rating scale used to measure the severity of depressive episodes in patients with mood disorders.[81]

8.2.2 CLINICAL GLOBAL IMPRESSION SCALES (CGI-S AND CGI-I)

The Clinical Global Impression (CGI) scales provide an assessment of illness severity and improvement over time.[82] The CGI-Severity (CGI-S) is used to rate the current severity of a participant's illness and the CGI-Improvement (CGI-I) is used to assess overall change in a participant's clinical status over time as a measure of treatment response or improvement.

8.2.3 CREDIBILITY/EXPECTANCY QUESTIONNAIRE

The Credibility/Expectancy Questionnaire (CEQ-CR) assesses participants' treatment expectancy (i.e., how much they expect to improve).[83]

8.2.4 MULTIDIMENSIONAL PSYCHOLOGICAL FLEXIBILITY INVENTORY

The Multidimensional Psychological Flexibility Inventory (MPFI) is an instrument used to assess psychological flexibility and inflexibility. It will be used to assess change in psychological flexibility at the end of the study.[84]

8.2.5 PERCEIVED STRESS SCALE

The Perceived Stress Scale (PSS) assesses participant's perceived stress and will be used to measure changes in perceived stress at the end of the study.[85]

8.2.6 30-ITEM MYSTICAL EXPERIENCE QUESTIONNAIRE

The 30-item Mystical Experience Questionnaire (MEQ-30) assesses an individual's mystical experience during a psychedelic dosing session.[86]

8.2.7 THE COMPUTERIZED NIH TOOLBOX (V3)

The Computerized NIH Toolbox (V3) offers a fully remote automated digital platform that assesses neurocognitive and behavioral functioning using an iPad-based battery of psychological tests.[87] The Cognitive and Psychological Wellbeing batteries will be used for cognitive subtyping.

8.3 SAFETY ASSESSMENTS

8.3.1 CUMULATIVE ILLNESS RATING SCALE

The Cumulative Illness Rating Scale (CIRS) is a tool used to assess the overall health burden of the participants, by evaluating the severity of illnesses across multiple organ systems.[76]

8.3.2 SWISS PSYCHEDELIC SIDE EFFECTS INVENTORY

The Swiss Psychedelic Side Effects Inventory (SPSEI) is a standardized tool assessing specified side-effects (i.e. severity, impact, duration, and treatment-relatedness) associated with the administration of psychedelics.[88]

8.3.3 PHYSICAL EXAMINATION, HEIGHT, AND WEIGHT

A full physical examination will be performed at Screening to include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system.

An abbreviated physical exam will be performed at Study Part B Re-Administration Baseline only if a change has been indicated over the course of the study. The abbreviated physical examination will focus on body systems involved in previous findings and any newly reported symptoms or AEs, as well as a standard physical examination of the heart, lungs, abdomen, and nervous system screen.

8.3.4 VITAL SIGNS

Vital signs will include temporal body temperature (°F), O_2, HR and BP.

8.3.5 ELECTROCARDIOGRAM

Standard 12-lead Electrocardiogram (ECG) will be measured after the participant has been semi-supine for at least 3 minutes. ECG outputs will include HR, cardiac rhythm, PR interval, QRS interval, QT interval, and QTcF (interval between Q and T wave corrected for heart rate using Fridericia's formula) interval.

8.3.6 CLINICAL LABORATORY TESTS (BLOOD AND URINE)

The following clinical laboratory tests are to be performed as indicated in the SOA:

- Complete blood count (CBC) with differential
- Comprehensive metabolic panel (CMP)
- Thyroid-stimulating hormone (TSH)
- Other:
    - Urine drug tests
    - Urine pregnancy test for participants of child-bearing potential
    - Urinalysis dip test

8.3.7 COLUMBIA-SUICIDE SEVERITY RATING SCALE

The Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidal ideation and behavior.[89]

8.3.8 CHALLENGING EXPERIENCES QUESTIONNAIRE

The Challenging Experiences Questionnaire (CEQ-CH) evaluates challenging experience(s) with psychedelics (i.e. panic or fear, grief, isolation, feeling as though one is dying, feeling insane, physiological distress, and paranoia).[90]

8.3.9 FACILITATOR DOSING DAY MONITORING FORM

The USONA Facilitator Dosing Day Monitoring Form (Appendix C) assesses occurrences (i.e. nausea and vomiting, acute physical distress, self-reported suicidal ideation) at specified time-points throughout the dosing session following the Dosing Day Vitals Guidance found in Appendix E.

8.3.10 PARTICIPANT RELEASE EVALUATION

The USONA Participant Release Evaluation form will be completed by the Facilitators and the study clinician to evaluate and confirm whether the participant is physical and mentally ready to safely leave the research facility accompanied by their support person. (Appendix C)

8.3.11 ADVERSE EVENTS AND CONCOMITANT MEDICATIONS

All AEs occurring after the participant signs the ICF and up to End of Trial will be recorded in the eCRF. Over the counter, supplements and prescribed medications will be recorded at each study visit on the concomitant medication log.

8.3.12 MRI SCREENING FORM

The MRI Screening Form is a self-report measure used to ensure a participant is safe for MRI imaging.

8.4 OTHER ASSESSMENTS

8.4.1 FACILITATOR APPROACH CHECKLIST

The USONA Facilitator Approach Checklist will be completed by the Facilitators as they work with the study participant through preparation, dosing day and integration sessions. (Appendix C)

8.4.2 FACILITATOR PREPARATION CHECKLIST

The USONA Facilitator Preparation Checklist provides instructions and documentation to ensure that all necessary components of the preparation session are completed. (Appendix C)

8.4.3 FACILITATOR INTEGRATION CHECKLIST

The USONA Facilitator Integration Checklist provides instructions and documentation to ensure that all necessary components of the integration sessions are completed. (Appendix C)

8.4.4 EMPATHY PROTOCOL

The Explanatory Models in Psychedelic-Assisted Therapy (EMPATHY) is a semi-structured qualitative interview developed by our research team based on the Kleinman Explanatory Model of Illness (EMI) (Appendix DAppendix D). As noted above, EMI is a framework in medical anthropology for understanding how patients' cultural beliefs shape their perception, experience, and response to illness, focusing on their ideas about causes, onset, severity, effects, and desired treatments, contrasting with the clinician's biomedical view to improve cross-cultural communication and care. This model uses specific questions (e.g., "What do you call the problem?", "What do you fear most?") to elicit the patient's personal meaning. In the proposed study, the goal is to assess whether (and how) PAT augmentation of antidepressant treatment changes their experience of depression and depression treatment. EMPATHY Interview 1 consists of 20 questions that assess a participant’s lived experience and narrative of their depressive illness that is intended to be conducted prior to treatment as a baseline assessment. EMPATHY Interview 2 consists of the same questions but asked from the perspective of whether the treatment impacted the participant’s responses.

8.4.5 ACCEPTABILITY OF INTERVENTION MEASURE (AIM), INTERVENTION APPROPRIATENESS MEASURE (IAM) AND FEASIBILITY OF INTERVENTION MEASURE (FIM)

The AIM, IAM and FIM are implementation science measures assessing perceptions of an intervention in terms of how well an intervention is received, is perceived as suitable and is practical to deliver from the perspective of participants and clinicians.[91]

8.5 BIOMARKERS

8.5.1 MRI SEQUENCES

Below is a list of specific MRI sequences. Additional physiological metrics will be acquired while the participants are inside the MRI by making use of eye recording, respiratory belt, pulse oximeter, and motion monitoring. Continuous monitoring of participants' eyes will be used in order to check for periods of prolonged eye closure, potentially indicating sleep. Real-time head motion monitoring will be done using the FIRMM software package already installed on our MRI scanners.[92]

8.5.1.1 STRUCTURAL MRI

Structural imaging will include high-resolution T1-weighted (0.8 mm) and T2-weighted (0.8 mm) images. These data will be used for accurate cross-subject registration and anatomical segmentation for surface-based analyses, as in Gordon, et. al, 2017.[93]

8.5.1.2 FUNCTIONAL MRI

Functional imaging will include 5 x 10-minute BOLD fMRI resting runs and 2 x 7.5 min runs each of 2 tasks during each session. The BOLD fMRI sequence will be a multi-band, multi-echo sequence designed to maximize cortical and subcortical SNR.[94, 95] During rest runs, participants will be instructed to visually fixate on a white crosshair presented against a black background. Two block-design task paradigms used in the Human Connectome Project (HCP) will be performed during the other fMRI runs.[96] One task is a gambling task originally developed by Delgado et al (2000)[97] that provides monetary reward, loss, or neutral feedback on each cued response. The other task is an emotional processing task originally developed by Hariri et al.[98] This task asks participants to match either emotional faces or neutral shapes on each trial. We will monitor patients as described above to ensure that they remain awake during these scans. The goal is to acquire at least 30 minutes of usable resting data at each visit, which is necessary to measure cortico-subcortical networks in individuals.[99] We propose 50 minutes of resting fMRI at each session based on an assumption that aggressive cleaning (framewise displacement > 0.2mm) may remove as much as 25% of data in the psychedelic condition.[39]

8.5.2 PROTEOMICS & BLOOD STORAGE

Participants will be asked to provide blood samples at 8 timepoints during Study Part A (Screening Visit, Baseline Visit, 3 times on Dosing Day, Trial Day 8, Trial Day 15, and Trial Day 30) and 7 timepoints during Study Part B (Baseline Visit, 3 times on Dosing Day, Trial Day 8, Trial Day 15, and Trial Day 30). Approximately 30 mL of blood will be obtained from each subject at each timepoint. Blood samples will be used to assess SASP and other as-yet-undetermined blood-based markers.

Remaining blood collected as part of the mandatory assessments as per the SOA (Section 1.3) may be stored for future, yet to be determined analysis, to contribute to the understanding of MDD or other diseases, the development of related or new treatments, and/or research methods.

8.6 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.6.1 DEFINITION OF ADVERSE EVENTS (AE)

Per 21 CFR 312.32(a), an AE is “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.” An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug. In the context of studying drugs with central nervous system activity, AEs should also include central nervous system events that are a change from baseline and are not necessarily experienced as untoward by participants. These may include experiences of euphoria, relaxation, or other potentially desirable effects. Review of AEs that may be abuse-related will inform the overall assessment of human abuse potential of the trial drug.

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

BP and HR that meet 1 of the following criteria may be considered an AE for the purposes of this trial:

- SBP >160 mmHg, sustained for ≥15 minutes.
- DBP >110 mmHg, sustained for ≥15 minutes.
- Elevated HR, defined by pulse ≥140 BPM, sustained for ≥15 minutes.

The AE terms listed below are MedDRA preferred terms which may be used to provide abuse-related information about the IP:

- 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.
- Related terms not captured elsewhere: drug tolerance; habituation; drug withdrawal syndrome; substance-related disorders.

An Investigator may provide an AE narrative, if deemed supportive, for AEs with MedDRA preferred terms related to suicidal ideation, suicidal behavior, HPPD, and/or an AE which may provide abuse-related information.

8.6.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6.3 DEFINITION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

Unexpected adverse reactions are considered Suspected Unexpected Serious Adverse Reactions (SUSARs) if the following 3 conditions are met:

1. The event must be serious (see Section 8.6.2)

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
3. The adverse reaction must be unexpected.

8.6.4 CLASSIFICATION OF AN ADVERSE EVENT

8.6.5 SEVERITY OF EVENT

Each AE will be classified according to the following criteria, with the exception of BP and HR elevations that will be classified per the guidelines in Table 8.1:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

Table 8.1: Guidelines for Severity Classification of Blood Pressure and Heart Rate Elevations

Parameter	Severity	Definition
Systolic Blood Pressure	Mild	>160 mmHg, sustained for ≥15 minutes, with no associated symptoms or need for clinical intervention.
	Moderate	>180 mmHg, sustained for ≥15 minutes, with no associated symptoms or need for clinical intervention.
	Severe	>180 mmHg, sustained for ≥15 minutes, with associated symptoms felt to be related to the BP elevation and/or need for clinical intervention.
Diastolic Blood Pressure	Mild	>110 mmHg, sustained for ≥15 minutes, with no associated symptoms or need for clinical intervention.
	Moderate	>130 mmHg, sustained for ≥15 minutes, with no associated symptoms or need for clinical intervention.
	Severe	>130 mmHg, sustained for ≥15 minutes, with associated symptoms felt to be related to the BP elevation and/or need for clinical intervention.
Heart Rate	Mild	>140 BPM, sustained for ≥15 minutes, with absent to mild associated symptoms or need for clinical intervention.
	Moderate	>140 BPM, sustained for ≥15 minutes, with moderate associated symptoms felt to be related to the tachycardia and/or need for clinical intervention.
	Severe	>140 BPM, sustained for ≥15 minutes, with severe associated symptoms felt to be related to the tachycardia and/or need for clinical intervention.
Abbreviation: BPM = beats per minute		

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

8.6.6 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.6.7 EXPECTEDNESS

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

8.6.8 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the AE eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.6.9 ADVERSE EVENT REPORTING

AEs will be reported following Washington University Human Resource Protection Office (HRPO) guidelines.

8.6.10 SERIOUS ADVERSE EVENT REPORTING

Study staff will report any serious adverse event to HRPO, whether it is considered related to the study intervention or not, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event, within 48 business hours of learning of the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center and should be provided as soon as possible.

The PI will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the PI's initial receipt of the information. In addition, the PI must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting.

8.6.11 REPORTING EVENTS TO PARTICIPANTS

Any Serious Adverse Events related to psilocybin will require an update of the study's consent form, and study participants will need to be re-consented with this new information.

8.6.12 EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the trial intervention. AEs that would otherwise meet the protocol definition of an AESI, but that occur prior to the first trial intervention (i.e., not treatment-emergent) or do not represent a worsening of clinical status after dosing the trial intervention, should not be reported as AESIs.

AESIs are to be reported within 72 hours of Investigator awareness. AESIs that are also SAEs are to be reported within 24 hours of Investigator awareness (see Section 8.6.2). AESIs will be assessed through thorough assessments of AEs at each specified visit.

The AESIs for this trial include:

- Suicidal ideation and behavior as defined in this protocol as the presence of 1 or more of the following, with confirmation by the Investigator's clinical assessment:
    - C-SSRS (Since Last Visit):
        - Answering "Yes" to questions 2, 3, 4, or 5 on the Suicidal Ideation portion (i.e., endorsing non-specific active suicidal thoughts; active suicidal ideation with any methods (not plan) without intent to act; active suicidal ideation with some intent to act, without specific plan; or active suicidal ideation with specific plan and intent), or
        - Answering "Yes" to questions 1, 3, 4, or 5 on the Suicidal Behavior portion (i.e., endorsing actual attempt; interrupted attempt; aborted attempt; or preparatory acts or behavior).
    - Verbal report of clinically significant suicidal ideation or behavior to Investigator.
- Prolonged visual perceptual effects, defined as effects occurring ≥24 hours after dosing.
- Dissociation, including derealization and depersonalization, defined as effects occurring ≥24 hours after dosing.

Additional solicited AEs include:

- Headache
- Nausea
- Elevated BP as defined by SBP >140 mmHg or DBP >90 mmHg on three separate readings and requiring medication
- Elevated HR as defined as >100 BPM and requiring medication

Visual perceptual effects, suicidal ideation verified by clinical assessment, headache, nausea, and overdose with suicidal intent will be reported through normal AE/SAE mechanisms. Elevated BP and heart rate will only be reported as an AE should medication be needed.

The AESIs criteria for visual perceptual effects and derealization are presented in Table 8.2.

Table 8.2: Adverse Events of Special Interest Criteria for Visual Perceptual Effects and Derealization

Adverse Event	Timing	Adverse Event of Special Interest (Yes/No)
Visual Perceptual Effects	Within 24 hours after IP dosing	No
	≥ 24 hours after IP dosing	Yes
Dissociation, including Derealization and Depersonalization	Within 24 hours after IP dosing	No
	≥ 24 hours after IP dosing	Yes

8.6.13 REPORTING OF PREGNANCY

If a participant becomes pregnant during the trial the investigator will make every effort to follow the participant until an outcome is known (i.e., spontaneous miscarriage, elective termination, normal birth). This includes following live births for a minimum of 30 days or to the first well-baby visit. Any adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with trial procedures. If

the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that of an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 8.6.8.

For reports of pregnancy in the female partner of a male participant, the CRF Pregnancy Report Form should be completed with the participant's identification number and year of birth, and details regarding the female pregnant partner should be entered in the narrative section.

8.7 UNANTICIPATED PROBLEMS

8.7.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

HRPO considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.7.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC/lead PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported in accordance with the Washington University IRB timeline.

8.7.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any unanticipated problems related to psilocybin will require an update of the study's consent form, and study participants will need to be re-consented with this new information.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study is an exploratory pilot designed to evaluate feasibility, safety, and preliminary clinical and neurobiological outcomes following psilocybin-assisted therapy. The study is not powered for confirmatory

hypothesis testing. Analyses will focus on descriptive statistics and estimation of treatment effects and variability to support interpretation of preliminary findings and inform future study design.

9.2 SAMPLE SIZE DETERMINATION

The planned enrollment of approximately 50 participants was selected to permit estimation of treatment effects and variability while enabling systematic evaluation of feasibility and safety outcomes. This sample size is expected to provide adequate precision to guide planning of a subsequent confirmatory study.

Feasibility metrics to be evaluated include recruitment and retention rates, dosing tolerability, and imaging data completeness.

9.3 POPULATIONS FOR ANALYSES

The safety population is defined as all participants who receive at least one dose of psilocybin. The safety population will include all participants who receive at least one dose of psilocybin and will be used for safety analyses. The analysis population will include participants who receive psilocybin and complete a baseline assessment and at least one post-dose assessment of the relevant outcome measure. Participants who discontinue early will be included in analyses to the extent that outcome data are available.

STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Outcomes will be summarized using appropriate descriptive statistics. Change-from-baseline measures will be calculated for relevant endpoints. Repeated measures over time may be evaluated using linear mixed-effects models with participant included as a random effect, as appropriate.

MRI Processing and Analysis

Functional MRI data will be preprocessed using a previously validated pipeline that includes correction for slice timing, head motion, spatial normalization to standard atlas space, and standard nuisance regression procedures.

Resting-state analyses will include region-of-interest (ROI) and network-level functional connectivity measures derived from individual-specific parcellations. Task-based fMRI data will be analyzed using general linear models to estimate task-evoked activation contrasts.

Whole-brain analyses will apply appropriate correction for multiple comparisons. Imaging quality control metrics will be summarized descriptively.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary endpoints are change-from-baseline measures in depressive symptom severity (MADRS total score) and psychological flexibility (MPFI score) following psilocybin-assisted therapy. Analyses will be conducted separately for Study Part A and Study Part B.

Change from baseline will be summarized at Day 2, Day 8, and Day 30. Exploratory repeated-measures models may be used to estimate mean change over time and associated confidence intervals.

Analyses will use the analysis population defined in Section 9.3. No formal multiplicity adjustment is planned.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Not Applicable

9.3.4 SAFETY ANALYSES

Safety analyses will include tabulation of adverse events by frequency, severity, and relatedness to study drug. The number and proportion of participants experiencing any adverse event, serious adverse event, or adverse event of special interest will be summarized. Vital signs and safety laboratory values will be summarized descriptively over time.

9.3.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics, including demographics and laboratory measurements, will be reported using descriptive statistics.

9.3.6 PLANNED INTERIM ANALYSES

No interim efficacy analyses are planned.

9.3.7 SUB-GROUP ANALYSES

No subgroup analyses are planned due to limited sample size.

9.3.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be maintained in secure systems and will be available for regulatory review and monitoring. No individual-level data will be publicly disseminated.

9.3.9 EXPLORATORY ANALYSES

Exploratory endpoints will be analyzed descriptively. Imaging and biomarker measures will use estimation-focused summaries and appropriate control.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

All personnel involved in the design and conduct of the research involving human participants will receive the required education on the protection of human research participants prior to the start of this project. Procedures to recruit participants for the protocol and obtain their informed consent or assent are by the P.I. Written informed consent will be obtained from all participants before any study procedures are initiated. The consent form, which incorporates HIPAA authorization, contains a description of the purpose and procedures, confidentiality, risks, procedures to minimize them, and possible benefits. Participants will be assured that participation in the study is completely voluntary, and that they are free to withdraw consent at any time and discontinue participation without prejudice to their current or future medical care. The objectives of the project, the requirements for participation, and any possible discomforts and risks will be clearly explained at each contact to the participants orally and in writing. All participants must sign an

informed consent form, indicating their consent and/or assent, approved by the WUSM Institutional Review Board, before they can participate in the study.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Verbal consent will be obtained at telephone screenings, via a Washington University IRB approved phone script. Verbal consent will grant permission for the study team to ask questions related to participant's health and PHI that will be relevant to screening inclusion/exclusion criteria for the study.

Written consent will be obtained prior to the start of any research activity, via a Washington University IRB informed consent form.

The following consent materials are submitted with this protocol: Consent Form and Telephone Assent Form used for Telephone screens (Appendix I).

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

All telephone screenings will be preceded by obtaining verbal consent from the potential screening participants using a WUSM IRB-approved phone screen document that gives a brief overview of the study and asks the potential participant's verbal permission to ask questions related to their health and PHI that will be relevant to screening inclusion/exclusion criteria for the study

Participants will be asked to read and review the IRB-approved consent document. A study team member will explain the research study to participants and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, potential risks and benefits of the study, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form, ask questions prior to signing, and have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. Participants will be informed that participation is voluntary, and that they may withdraw from the study at any time, without prejudice. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A copy of the informed consent document will be given to the participants for their records.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the principal investigator will promptly inform study participants, and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by all members of the research team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

Representatives of the Washington University's IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and Institutional policy requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the secured, centralized database. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Washington University research staff will be secured and password protected.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Washington University. After the study is completed, the de-identified, archived data will be stored at Washington University for use by other researchers including those outside of the study. Permission to transmit data to other researchers will be included in the informed consent.

See also **Section 10.1.3, Confidentiality and Privacy** and **Section 10.1.9, Data Handling and Record Keeping**, for further information on future use of study records.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Ginger Nicol, MD	Eric Lenze, MD
Washington University School of Medicine	Washington University School of Medicine
Campus Box 8134, 600 South Taylor, St. Louis, MO 63110	Campus Box 8134, 600 South Taylor, St. Louis, MO 63110
314-362-5154	314-362-5154
nicolg@wustl.edu	lenzee@wustl.edu

Key Personnel

Ginger Nicol, MD, Professor of Psychiatry and Director of the Center for Holistic Interdisciplinary Research in Psychedelics (CHIRP) – Principal Investigator. Experienced as principal investigator on clinical trials in Psychiatry in a variety of novel interventions including pharmacological (relevant examples include ketamine, psilocybin and kappa opioid antagonists in depression), and behavioral interventions.

Eric Lenze, MD, Chair of Psychiatry; geriatric psychiatrist, expert in treatment resistant depression and clinical trialist with 20+ years of experience leading multisite clinical trials using precision outcome measures like neuroimaging and blood biomarkers, including in clinical trials of ketamine and psilocybin.

Leopoldo J. Cabassa, PhD Co-investigator with expertise in implementation science, 20+ years of experience in developing, adapting and testing behavioral interventions for psychiatric conditions; co-director of CHIRP and trained in psychedelic-assisted therapy. He will work with the team to adapt and refine the psychotherapeutic approach and will be responsible for training and fidelity-monitoring with study therapists.

Tim Laumann, MD, PhD – Co-Investigator; Dr. Laumann is a neuroscientist with a focus in Precision Functional Mapping. He will lead the neuroimaging component of the study guiding the imaging technicians on data collection, cleaning and analysis.

Breno Diniz, MD, PhD – Co-Investigator; Dr. Diniz is an Associate Professor of Psychiatry at the UCONN Center of Aging at the University of Connecticut. He is a geroscientist who developed the Senescence-Associated Secretory Phenotype (SASP) Index and has deep knowledge of biomarker panel development and biotyping methods that combine genomic, proteomic, neuroimaging, cognitive, clinical, and demographic data.

10.1.6 SAFETY OVERSIGHT

The Principal Investigator (PI), Ginger Nicol, MD, is responsible for overall study conduct and participant safety. A designated Medical Monitor, Eric Lenze, MD, will provide independent medical oversight and review safety data throughout the study.

The PI and Medical Monitor will review adverse events, protocol deviations related to participant safety, and emergent clinical concerns on an ongoing basis. The Medical Monitor has the authority to recommend protocol modifications, temporary suspension of enrollment, or study termination if participant safety concerns arise.

Study personnel with clinical responsibilities are trained in the recognition and management of acute psychological distress and medical adverse events associated with psilocybin administration. Safety oversight is integrated with the Data and Safety Monitoring Plan described above.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that reported trial data are accurate, complete, and verifiable, and that trial conduct complies with the approved protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

Washington University will provide training, site monitoring, and data management. Monitoring activities will include periodic reviews of informed consent documentation, verification of eligibility, source data verification, safety reporting, protocol compliance, and data accuracy. Monitoring will occur at regular intervals determined by study risk and enrollment activity. Findings will be documented and

communicated to the study team, and corrective actions will be implemented as needed to maintain compliance and data integrity.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Our site will perform internal reviews of quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe quality management.

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

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

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of Drs. Nicol and Lenze, who will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by Washington University's Institute for Informatics. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Participation in this study will be kept confidential and the participant's name will not be made known to anyone other than clinical personnel. No participant will be identified in any report or publication about this study. Cross-walks linking the research identifier code to participant identifying information will be restricted to only those members of the research team who require access to this information to conduct the study. Every effort will be made to keep research records private. However, if disclosure of records including personal information is ever legally required, we will take all steps allowable by law to protect the privacy of personal information. To ensure the privacy and confidentiality, all data collected at WUSM

is securely stored on WUSM servers. Data uploads will be on the secure production servers, which are accessible only to key personnel, and will be monitored regularly under the direction of Drs. Nicol & Lenze.

The database management for WUSM data will be built with multiple layers of security, following best practices and WUSM requirements for securing sensitive data. The data utilized in the proposed work will be de-identified and stored according to institutional protection standards. Participants will be assigned a unique, study specific participant identifier (ID); this number alone will be used to identify all study information. All study data will contain only the participant's unique study identification number from the parent study, using a reference system maintained by the PI to link de-identified data back to the original data source. No information about the participants will be provided to anyone (except in emergencies as defined above) in person or by telephone, except as required by law.

The main levels of security for electronic data at WUSM include:

a. Project computers are all password protected, are protected by the WUSM firewall, and in locked offices within a building having limited, electronic passkey access. Data will not be accessible to the internet or contained on laptop computers.
b. Password protection will be used in additional places at the server and web portal levels for all transactions that allow entry and editing of data, provide access to sensitive subject data or administrative privileges. Passwords will be managed to require all users to change their password within 90 days and strict rules will be implemented to require strong passwords.
c. All data hosted on WUSM servers will be limited to PIs and key members of the research team. Prior to receiving server access, researchers must demonstrate the completion of HIPAA training and abide by security procedures developed by the IT staff at WUSM.
d. The production servers at the WUSM facility will be housed in a dedicated computer machine room containing emergency backup power, a UPS, a non-liquid fire suppression system and authorization-based limited access. The computer and corresponding disk storage will be locked in a computer cabinet within the computer room with keys only distributed to key personnel under the supervision of Dr. Nicol.
e. According to industry best practices, all software services and corresponding ports on the servers that are known to be substantial security risks, and which are not used by the project data management resources will be disabled. Furthermore, all databases will reside behind WUSM firewalls.

The MRI studies presented in this work will be carried out in part in the East Building MR Facility of the Washington University Medical Center. The Shared Data Storage is a ZFS (zettabyte file system) based Radiology research Storage System that supports the data storage needs of radiology research. The ZFS solution is comprised of two separate systems – a production system and an archive system. The 1 petabyte “live” production system is used for the storage of data that is currently being processed or with immediate and unpredictable access needs. The archive solution is for the deep-archiving of data with no immediate access needs.

The ZFS production system is comprised of both primary and disaster recovery (DR) hardware. The primary system has been engineered as a fully redundant system, and no single hardware component failure will cause the system to fail. The system is currently configured to provide approximately 1PB of usable storage. Solid state technology is used as both read-and-write cache to enhance performance. The backend near-line SAS storage is configured as RAID7 to ensure data reliability and integrity.

Data is replicated every 30 seconds from the primary system to the physically disparate DR system. Snapshots of data that has been changed or deleted on the ZFS system are taken five nights a week. Thirty snapshots or 6 weeks of changed data are stored insuring that any accidental changes or deletions of data can be recovered.

The ZFS archive system is comprised of low-speed disks. These disk arrays will be powered down and only brought online when data retrieval is needed.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

We will follow the reporting guidelines provided by Washington University in St. Louis HRPO.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study will be made available on openfmri.org[107] as a resource for neuroscientists.

10.1.12 CONFLICT OF INTEREST POLICY

We will follow Washington University in St. Louis' Conflict of Interest policy.

10.2 ADDITIONAL CONSIDERATIONS

DEA License Information:

DEA Number: RN0572075
This DEA Number is ACTIVE
Name (Last, First): NICOL, GINGER E
Business Activity: RESEARCHER (I)
Business Address 1: 600 S. TAYLOR AVE.
Business Address 2: SUITE 121
Business Address 3: WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
City: SAINT LOUIS

State: MO
Zip: 63110
Schedules: Schedule I,
Fee Status: Paid
Drug Codes: 7437 Bulk Drug Codes:
Expire Date: 10-31-2026

10.3 ABBREVIATIONS

Abbreviation	Definition
ADHD	attention-deficit/hyperactivity disorder
AE(s)	Adverse Event(s)
AESI	adverse event of special interest
AIM	Acceptability of Intervention Measure
ANOVA	Analysis of Variance
ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
BOLD	blood oxygenation level dependent
BP	blood pressure
BPM	beats per minute
BJC	Barnes Jewish Christian Hospital
CBC	complete blood count
CDR	Code of Regulations
CEN	central executive network
CEQ - CR	Credibility/Expectancy Questionnaire
CEQ - CH	Challenging Experiences Questionnaire
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CHIRP	Washington University Center for Holistic Interdisciplinary Research in Psychedelics
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CITI	Collaborative Institutional Training Initiative
CMP	Comprehensive metabolic panel
CRF	Case Report Form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DBS	deep brain stimulation
DCC	Data Coordinating Center
DEA	Drug Enforcement Administration
DMN	default mode network
DMT	N,N-dimethyltryptamine
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	Electronic Case Report Forms

EMPATHY	Explanatory Models in Psychedelic-Assisted Therapy
FC	Functional brain connectivity
FD	frame-wise displacement
FDA	Food and Drug Administration
FIM	Feasibility of Intervention Measure
FIRMM	Framewise Integrated Real-time MRI Monitoring
fMRI	Functional Magnetic Resonance Imaging
FOCBP	female of childbearing potential
FWHM	full-width half max
GCP	Good Clinical Practice
GLM	Generalized linear model
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HCP	Human Connectome Project
HIPAA	Health Insurance Portability and Accountability Act
HML	Healthy Mind Lab
HPA	hypothalamic-pituitary-adrenal
HPPD	Hallucinogen persisting perception disorder
HR	Heart rate
HRPO	Washington University Human Resource Protection Office
ID	identification
IB	Investigator's Brochure
IAM	Intervention Appropriateness Measure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IL-6	interleukin-6
IND	Investigational New Drug Application
IP	investigational product
IRB	Institutional Review Board
LOA	Letter of Authorization
LSD	lysergic acid diethylamide
LTFU	long-term follow-up
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitors
MD	Doctor of Medicine
MDD	major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities

MEQ-30	30-Item Mystical Experience Questionnaire
MIR	Mallinckrodt Institute of Radiology
mPFC	medial prefrontal cortex
MPFI-24	Multidimensional Psychological Flexibility Inventory
MO	Missouri
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
NIHT-CFB	National Institutes of Health Toolbox – Cognitive Battery
NIL	Neuroimaging Laboratories
NIL-RC	Neuroimaging Labs Research Center
O_2	Oxygen saturation
PAT	Psilocybinassisted therapy
PCP	Primary care provider
PCP	Phencyclidine
PFM	Precision brain mapping
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PR	interval from the beginning of the P wave to the beginning of the QRS complex
Prep	Preparation
PSQ	Psychosis Screening Questionnaire
PSS	Perceived Stress Scale
PT	prothrombin time
QC	Quality Control
QRS	combination of the Q wave, R wave and S wave, representing ventricular depolarization
QT	interval between Q and T wave
QTcF	interval between Q and T wave corrected for heart rate using Fridericia's formula
RF	Radiofrequency
ROI	regions of interest
RR	respiratory rate
SAE	Serious Adverse Event
SAS	Serial Attached SCSI
SASP	Senolysis-associated secretory phenotype
SBP	systolic blood pressure
SCID-5-CT	Structured Interview for DSM-5 Disorders-Clinical Trials Version
sqACC	subgenual cingulate or subgenual anterior cingulate cortex
SIRT1	sirtuin 1
SN	salience network

SPSEI	Swiss Psychedelic Side Effects Inventory
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SSRI	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Temp	Temperature
TMS	transcranial magnetic stimulation
TRD	treatment-resistant depression
TSH	thyroid stimulating hormone
UDP	uridine diphosphate
UDS	Urine drug screen
UGT	uridine diphosphate glucuronosyltransferase
UP	Unanticipated Problem
US	United States
USONA	Usona Institute
VNS	vagus nerve stimulation
WUSM	Washington University in St. Louis School of Medicine
WUSTL	Washington University in St. Louis
ZFS	zettabyte file system
5-HT_{2A}	5-hydroxytryptamine 2A receptor
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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sponsor, supervised the conduct of the trial under the direction of the sponsor. An independent contract research organization (Worldwide Clinical Trials) were responsible for conducting MADRS assessments with blinded remote raters. The analysis of the data was performed by the contract research organization (Worldwide Clinical Trials); and the interpretation of the data was performed by the sponsor. GMG has consulted for Beckley Psytech, Boehringer Ingelheim, Clerkenwell Health, EVApharm, H Lundbeck A/S, Janssen Global Services, Novartis, Ocean Neurosciences, P1vital, Sage Therapeutics, Servier, Takeda and WebMD. GMG, MC, LM, SM, HS, CS, SCS, JT, SW, and EM are current or past employees of COMPASS Pathfinder. GMG, MC, LM, SM, HS, CS, JT, SW, and EM own shares or options in

COMPASS Pathfinder. DF has received grant funding from MindMed, Neurolief, Perception Neuroscience, and Relmada Therapeutics. DF holds a patent for psychedelic drug treatment of neuropsychiatric disorders and cerebral palsy. DF, JRK, VOK, and SK-P were site investigators or sub-investigators for COMPASS Pathfinder during the clinical trial and received funding to conduct the study, and SK-P is a consultant for COMPASS Pathfinder, providing therapist training and mentorship, and clinical development. JRK has consulted for Clerkenwell Health and has received grant funding from the Health Research Board (ILP-POR-2022-030).

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12 LIST OF APPENDICES

Appendix A. USONA Investigator's Brochure

Appendix B. USONA PSIL301 Study Protocol

Appendix C. USONA Clinical Facilitator Manual

Appendix D. EMPATHY Interview Protocol

Appendix E. Dosing Day Vitals Guidance

Appendix F. Contraception and Barrier Guidance

Appendix G. List of prohibited Medications

Appendix H. Therapeutic Dose Ranges for Allowed Antidepressant Monotherapy

Appendix I. Consent form and Telephone Screen Assent Form