Protocol and Synopsis MPG1
IND #063384

An Open-Label Feasibility and Safety Study of MDMA-Assisted Group Therapy for the Treatment of Posttraumatic Stress Disorder in Veterans

COMPOUND	3,4-methylenedioxymethamphetamine (MDMA)
BRIEF TITLE	MDMA-Assisted Group Therapy for PTSD
STUDY PHASE	Phase 2
STUDY NUMBER	MPG1
SPONSOR NAME	Multidisciplinary Association for Psychedelic Studies (MAPS)
SPONSOR DESIGNEE	Amy Emerson Chief Executive Officer MAPS Public Benefit Corporation
REGISTRY ID	NCT #: TBD
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Disclaimer: This protocol version is for public viewing. Some information has been removed to maintain the integrity of this ongoing study.

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List of Abbreviations

°C	Degrees Celsius
ACE	Adverse Childhood Experiences Questionnaire
ADHD	Attention Deficit/Hyperactivity Disorder
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AGPA	American Group Psychotherapy Association
ALT	Alanine Aminotransferase
AMI	Acute Medical Infarction
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AxMP	Auxiliary Investigational Medicinal Product
BDI-II	Beck Depression Inventory-II
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAPS-4	Clinician-Administered PTSD Scale for DSM-4
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CSI	Cornell Services Index
C-SSRS	Columbia-Suicide Severity Rating Scale
DDIS	Dissociative Disorders Interview Schedule
DID	Dissociative Identity Disorder
dIGPP	Cohen's d Independent Groups Pre-test Post-test
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSP-I	Dissociative Subtype of PTSD Interview
DTE	Developmental Trauma Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECR-S	Experiences in Close Relationships-Short Form
ECT	Electroconvulsive Therapy
EDC	Electronic Data Capture
EMA	European Medicines Agency
EMDR	Eye Movement Desensitization and Reprocessing
EQ-5D-5L	EuroQol Five Dimensions-Five Levels Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GMP	Good Manufacturing Practice
GQ	Group Questionnaire
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal
HPQSF	Health and Work Performance Absenteeism and Presenteeism Short Form

IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committees
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IR	Independent Rater
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
kg	Kilogram
L	Liter
LAR	Legally Authorized Representative
LEC-5	Life Events Checklist
LTFU	Long-term Follow-up
MAPS	Multidisciplinary Association for Psychedelic Studies
MPBC	MAPS Public Benefit Corporation
MAOI	Monoamine Oxidase Inhibitor
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
mg	Milligram
mITT	Modified Intent-to-Treat
mmHg	Millimeters of Mercury
mmol	Millimolar
MMRM	Mixed Model Repeated Measure
MPBC	MAPS Public Benefit Corporation
ms	Millisecond
NIMP	Non-Investigational Medicinal Product
PABP	Person Able to Become Pregnant
PAC	Premature Atrial Contractions
PCL-5	PTSD Checklist for DSM-5
PFC	Pre-Frontal Cortex
PI	Principal Investigator
PTSD	Posttraumatic Stress Disorder
PTGI	Posttraumatic Growth Inventory
PVC	Premature Ventricular Contractions
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SCID-5-SPQ	SCID-5 Self-report Personality Questionnaire
SCS	Self-compassion Scale
SDS	Sheehan Disability Scale
SGOT	Serum Glutamic Oxaloacetic Transaminase

SIB	Suicidal Ideation and Behavior
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SoA	Schedule of Activities
SSRI	Selective serotonin reuptake inhibitor
TBI	Traumatic Brain Injury
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid-stimulating Hormone
UFEC	Utilization of Facility-based and Emergent Care
U.S.	United States
UK	United Kingdom
VA	U.S. Department of Veterans Affairs
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization

1.0 Protocol Summary

1.1 Synopsis

Protocol Title

An Open-Label Feasibility and Safety Study of MDMA-Assisted Group Therapy for the Treatment of Posttraumatic Stress Disorder in Veterans

Brief Title

MDMA-Assisted Group Therapy for PTSD

Rationale

PTSD is a serious debilitating disorder that negatively impacts a person's daily life and affects United States military veterans at a much higher rate than the general population. MDMA has been shown to reduce defenses and fear of emotional injury, enhance communication, and increase empathy. MDMA may enhance fear extinction learning in humans. These subjective effects of MDMA create a productive psychological state that enhances the therapeutic process for the treatment of PTSD and other anxiety disorders. The acceptable risk-benefit ratio in early trials justified expansion in a Phase 3 program to further assess the efficacy and safety of this treatment in participants with moderate to severe PTSD. The sponsor has completed one of the two Phase 3 randomized, placebo-controlled, two-arm, double-blind, multi-site studies of three once-monthly Experimental Sessions of therapy combined with either a flexible divided-dose of MDMA or placebo, along with non-drug preparatory and integrative therapy. The second Phase 3 confirmatory study is currently ongoing.

Current clinical practice guidelines for the treatment of PTSD issued by the Department of Veterans Affairs and the Department of Defense recommend group therapy over no treatment, but make no specific recommendations regarding the type or use of group therapy in lieu of other interventions. Additionally, no randomized controlled clinical trials adhering to modern-day scientific rigor have yet examined the efficacy of MDMA-assisted group therapy.

To further assess the feasibility, efficacy, and safety of MDMA-assisted group therapy for participants with at least moderate PTSD, the sponsor is conducting a phase 2, open-label, non-randomized, 3-cohort study. This novel treatment package consists of two once-monthly Experimental Sessions of therapy combined with a divided-dose of MDMA, along with non-drug preparatory and integrative therapy administered in both individual and group sessions. The Primary Outcome measure, the Clinician Administered PTSD Scale (CAPS-5), evaluates changes in PTSD symptom severity and is assessed by a blinded centralized Independent Rater (IR) pool. The therapeutic approach will combine manualized MDMA-assisted therapy for PTSD with group therapy components.

The current FDA-guided protocol for individual patient MDMA-assisted therapy for PTSD, which requires numerous two-therapist sessions for each individual patient, may present accessibility challenges for some, particularly individuals with limited financial resources. A group therapy protocol, in which most of the therapy sessions are conducted in a group setting, would significantly decrease both the time and cost associated with treatment, further supporting accessibility and rapid post-approval dissemination. This study will explore the risk:benefit ratio of group therapy as compared to the individual therapy of MDMA-assisted therapy for PTSD.

Objectives and Endpoints

Objectives	Assessment Window	Endpoints
Primary		
Assess changes in PTSD symptom severity.	CAPS-5 (Baseline) and (Outcome)	CAPS-5
Secondary		
Assess changes in clinician-rated functional impairment.	SDS (Baseline) and (Outcome)	SDS
Safety		
Assess incidence of Treatment Emergent AEs (TEAEs) that may be indicative of a medical complication of MDMA, such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.	All visits following Experimental Session 1 (initial IMP administration)	AEs reported in eCRF
Assess incidence of AEs by severity.	All visits following enrollment	AEs reported in eCRF
Assess incidence of AEs by severity categorized as leading to discontinuation of IMP, resulting in death or hospitalization, or continuing at Study Termination.	All visits following enrollment	AEs reported in eCRF
Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function, suicidality, and abuse liability.	All visits following enrollment	AEs reported in eCRF
Assess incidence of SAEs.	All visits	SAEs reported in eCRF
Assess incidence of psychiatric concomitant medications taken.	Phone and Site Screening, all visits with exception of Preparatory Session 1 and (Outcome)	Medication review
Assess relative incidence of positive or serious ideation and suicidal behavior.	All site visits	C-SSRS
Assess mean changes in physiological measures.	Site Screening, Experimental Session 1 and Experimental Session 2 (pre-IMP administration and end of visit)	Blood pressure, heart rate, and body temperature
Exploratory		
Evaluate group cohesion within and between cohorts based on comparison of PTSD treatment outcome.	CAPS-5 (Baseline) and (Outcome)	CAPS-5
Assess changes in severity of dissociative symptoms associated with PTSD.	DSP-1 (Baseline (Outcome)	DSP-I
Evaluate the effect of adverse childhood experiences on PTSD treatment outcome as a covariate.	Preparatory Session 3 & Safety review, (Baseline), and (Outcome)	ACE CAPS-5
Characterization of PTSD severity with a descriptive time course plot.	Preparatory Session 3 & Safety review, , Integrative Session 1.4, and (Outcome)	PCL-5

Objectives	Assessment Window	Endpoints
Assess changes in severity of dissociative symptoms associated with PTSD treatment outcome.	CAPS-5 T1 (Baseline) and CAPS-5 T2 (Outcome)	DSP-I
Assess changes in group cohesion.	Preparatory Session 3 & Safety review, Integrative Session 1.4, Integrative Session 2.4, and Study Termination	GQ
Assess changes in depression symptoms.	Preparatory Session 3 & Safety review and Study Termination	BDI-II
Assess changes in attachment dynamics.	Preparatory Session 3 & Safety review and Study Termination	ECR-S
Assess changes in positive outcomes following trauma.	Preparatory Session 3 & Safety review and Study Termination	PTGI
Assess changes in perceived social support.	Preparatory Session 3 & Safety review and Study Termination	SPS
Assess changes in self-compassion.	Preparatory Session 3 & Safety review and Study Termination	SCS
Assess changes in health economics.	Preparatory Session 3 & Safety review and Study Termination	CSI
Assess changes in quality of life.	Preparatory Session 3 & Safety review and Study Termination	EQ-5D-5L
Assess changes in workplace productivity.	Preparatory Session 3 & Safety review and Study Termination	HPQSF

Overall Design

This Phase 2, open-label, non-randomized, 3-cohort study assesses the feasibility and safety of MDMA-assisted group therapy for the treatment of PTSD in veterans. The study will be conducted in up to N=18 participants, recruited in three cohorts of six participants and receive therapy sessions throughout their participation in these groups.

For each participant, the study will consist of:

- **Screening Period and Enrollment**: phone screen, informed consent, eligibility assessment, and enrollment of eligible participants.
- **Preparatory Period:** initiation of medication tapering, Preparatory Sessions, and baseline assessments.
- **Treatment Period**: two Experimental Sessions, and four Integrative Sessions following each Experimental Sessions.
- **Follow-up Period and Study Termination**: Primary Outcome assessment and Study Termination visit.

After the Screening Period and Enrollment, , eligible participants will begin a ~4-week Preparatory Period. Participants will attend four, 90-minute, non-drug, Preparatory Sessions,

including three group sessions and one individual session.. Following the Preparatory Period, participants will begin an ~8-week Treatment Period comprised of two Experimental Sessions, each followed by four Integrative Sessions.
MDMA will be administered twice during the Treatment Period: one Individual Session and one Group Session. The Experimental Sessions will last ~8 hours. Four 90-minute Integration Sessions, each one week apart, will follow the Individual Experimental Session. The first Integration Session will be Individual, occurring the morning following Experimental Session 1, and the other three will be Group Integration Sessions. Finally, four Group Integration Sessions, each a week apart, will follow the Group Experimental Session. Integrative Session 2.1 will take place the morning after Experimental Session 2. A study termination visit will be conducted at the end of the study.

Number of Participants and Study Duration
Approximately 60 participants will sign an ICF and be screened to achieve up to 18 participants (in 3 cohorts of up to 6) enrolled to study intervention.

Study details include:

- The study duration following initial screening will be up to 20 weeks.
- The treatment period duration will be up to approximately 10 weeks.
- The visit frequency will be approximately weekly.

Data Monitoring/Other Committee

A Data Monitoring Committee (DMC) will not be used for this open-label study.

2.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization and clinical trial sponsor working to obtain marketing approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to therapy in patients with posttraumatic stress disorder (PTSD). MAPS-sponsored studies are implemented through MAPS' wholly owned subsidiary and delegate, the MAPS Public Benefit Corporation (PBC), a small or medium-sized enterprise organization.

Controlled Phase 1 studies, nonclinical studies, Phase 2 and Phase 3 studies and investigator-initiated studies formed the basis for the Clinical Development Program of MDMA under the U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) #063384. MDMA-assisted therapy is an FDA Breakthrough-Designated treatment for PTSD based on the potential for substantial improvement over available medications.

2.1 Study Rationale

PTSD is a serious debilitating disorder that negatively impacts a person's daily life and affects United States military veterans at a much higher rate than the general population. MDMA has been shown to reduce defenses and fear of emotional injury, enhance communication, and increase empathy. MDMA may enhance fear extinction learning in humans. These subjective effects of MDMA create a productive psychological state that enhances the therapeutic process for the treatment of PTSD and other anxiety disorders. The acceptable risk-benefit ratio in early trials justified expansion in a Phase 3 program to further assess the efficacy and safety of this treatment in participants with moderate to severe PTSD. The sponsor has completed one of the two Phase 3 randomized, placebo-controlled, two-arm, double-blind, multi-site studies of three once-monthly Experimental Sessions of therapy combined with either a flexible divided-dose of MDMA or placebo, along with non-drug preparatory and integrative therapy. The second Phase 3 confirmatory study is currently ongoing.

Current clinical practice guidelines for the treatment of PTSD issued by the Department of Veterans Affairs and the Department of Defense recommend group therapy over no treatment, but make no specific recommendations regarding the type or use of group therapy in lieu of other interventions. Additionally, no randomized controlled clinical trials adhering to modern-day scientific rigor have yet examined the efficacy of MDMA-assisted group therapy.

To further assess the feasibility, efficacy, and safety of MDMA-assisted group therapy for participants with at least moderate PTSD, the sponsor is conducting a phase 2, open-label, non-randomized, 3-cohort study. This novel treatment package consists of two once-monthly Experimental Sessions of therapy combined with a divided-dose of MDMA, along with non-drug preparatory and integrative therapy administered in both individual and group sessions. The Primary Outcome measure, the Clinician Administered PTSD Scale (CAPS-5), evaluates changes in PTSD symptom severity and is assessed by a blinded centralized Independent Rater (IR) pool. The therapeutic approach will combine manualized MDMA-assisted therapy for PTSD with group therapy components.

The current FDA-guided protocol for individual patient MDMA-assisted therapy for PTSD, which requires numerous two-therapist sessions for each individual patient, may present accessibility challenges for some, particularly individuals from marginalized populations. A group therapy protocol, in which most of the therapy sessions are conducted in a group setting, would significantly decrease both the time and cost associated with treatment, further supporting

accessibility and rapid post-approval dissemination. This study will explore the risk:benefit ratio of group therapy as compared to the individual therapy of MDMA-assisted therapy for PTSD.

2.2 Background

2.2.1 Posttraumatic Stress Disorder (PTSD)

PTSD is a serious debilitating disorder associated with increased mortality and cardiometabolic morbidity. PTSD is a stress-related psychiatric condition that may occur following a traumatic event such as war, disaster, sexual abuse, violence, terrorism, and accidents. The four main symptom categories described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), include arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and nightmares. PTSD negatively impacts a person's daily life, resulting in fractured relationships, inability to maintain employment, diminished cognitive and psychosocial functioning, substance abuse, high-cost healthcare utilization, and increased depression and suicide risk. People who suffer from PTSD often relive the experience through nightmares and flashbacks, have poor sleep quality, and feel detached or estranged. Confronting overwhelming internal distress and frightening external environments can also lead to high levels of depersonalization and derealization, which led clinicians to identify a dissociative subtype of PTSD in the DSM-5. Adaptations in normal brain function have been observed in imaging studies of patients with PTSD that underlie alterations in emotional processing and regulation, cognition, and many aspects of behavior, though clinical symptoms and changes in brain activity are not homogenous across patients [1]. The dissociative subtype occurs in 12 to 30% of people with PTSD and is characterized by detachment and emotional numbing and visualized in the brain as overmodulation of affect mediated by midline prefrontal inhibition of limbic regions, while the non-dissociative subtype presents symptoms of hyperarousal and re-experiencing, an emotional under modulation mediated by the failure of prefrontal inhibition of the same limbic regions [2, 3]. Patients suffering from the dissociative subtype of PTSD typically have early childhood trauma and appear to be particularly difficult to treat, with mixed response to existing evidence-based treatments. PTSD affects United States military veterans many times more than the general population [4] and is estimated to cost the VA billions of dollars per year, including suicides, medical comorbidities, and lost productivity [5]. The link between interpersonal problems and PTSD symptoms among United States military veterans has been well-established in the literature [6, 7].

In Europe, lifetime PTSD prevalence ranges from 0.56% to 6.67% in the general population. The Netherlands was shown to be amongst the countries with the highest lifetime prevalence of PTSD next to the United Kingdom (UK), France and Germany [8]. The lifetime PTSD prevalence in the general population in the Netherlands is 7.4% [9], in the UK adult population, the lifetime prevalence is between 1.9 and 8.8% [10]. Occupational exposure to dangerous and high-risk situations increases the risk for PTSD. This applies to military personnel and police officers. In Dutch veterans the risk of developing PTSD is increased in the first 2 years after deployment [11] and the need for medical care is also increased [12]. In the UK, the cost of PTSD to the National Health Service and society is substantial, with a recent study in Northern Ireland estimating 150 million euro per year [13].

Available PTSD treatments, including medications and therapy, effectively treat only a fraction of people who try them for adequate dose and duration. This indicates a need to develop treatments targeting durable remission of PTSD. There are two pharmacotherapies approve for PTSD by the FDA and European Medicines Agency (EMA), both of which are selective serotonin reuptake inhibitors (SSRIs). Paroxetine and sertraline (Paxil and Zoloft) both demonstrated statistically

significant superiority over placebo on the CAPS in 12-week confirmatory clinical trials with daily dosing, but some studies were less effective in treating combat-related PTSD and sertraline demonstrated gender differences with minimal efficacy in men [14-16]. PTSD rarely remits after 12 weeks of SSRIs, and many patients who are placed on maintenance treatment experience partial relief of symptoms, which fully return upon discontinuation of treatment. Adverse effects of maintenance SSRI treatment that contribute to discontinuation include sexual dysfunction, weight gain, and sleep disturbance. Variable SSRI treatment outcomes have led to recommendations of trauma-focused therapy as routine first-line treatment by the VA's National Center for PTSD in the U.S., as well as by the World Health Organization (WHO). Currently, there is evidence that the antidepressants paroxetine, venlafaxine, sertraline and fluoxetine can be effective in post-traumatic stress disorder, but the magnitude of effect is, unfortunately, small to medium [17](Cohen's d=0.13–0.43) and there is no evidence for augmenting trauma-focused therapy with drugs, such as D-cycloserine, that have evidence for enhancing exposure therapy in other disorders [18]. An extensive list of medications, namely antipsychotics, anxiolytics, antidepressants, and sleep aids, are frequently prescribed off-label but are minimally effective in reducing PTSD symptoms.

Several meta-analyses of PTSD treatment have reported trauma-focused therapy results in greater sustained benefit in comparison to maintenance medication [19, 20]. Trauma-focused cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy are considered among the most effective therapies for the treatment of PTSD [21, 22]. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in reducing symptoms of PTSD for some people [21, 22], although many patients need more than one type of treatment to reduce or resolve those symptoms. A meta-analysis concluded that all treatments intended to be therapeutic, including those listed above, are similarly effective for PTSD [23]. One treatment approach is to develop medications and/or therapeutic treatments that may indirectly decrease or eliminate the neurochemical irregularities underlying chronic hyperarousal and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis associated with PTSD [24].

PTSD carries a high public burden, both economically and socially, by increased use of health and social services, lost wages, and disability payments [25, 26]. Given the chronicity of PTSD, low treatment compliance evidenced by high dropouts, and limited recovery with current medications contributing to serious outcomes, PTSD patients exhibit an unmet medical need.

2.2.2 Group Therapy

Outcome research has demonstrated that the efficacy of group therapy, involving one or more therapists working with a small number of patients within the same space, is at least equal to that of individual therapy [27]. The American Group Psychotherapy Association (AGPA) has developed clinical practice guidelines for assembling a group, conducting group therapy, and measuring clinical outcomes [28]. Irving Yalom (2005), who first published Theory and Practice of Group Psychotherapy in 1970, has derived 11 evidence-based therapeutic factors of group therapy [29]. Examples include interpersonal learning, development of socialization techniques, universality, instillation of hope, and group cohesiveness. Interpersonal learning allows group members to give and receive feedback with peers in order to gain a greater understanding of themselves, and development of socialization techniques involves real-time interaction with peers in a controlled environment with direct observation and guidance from the group therapist(s). Universality allows individuals with similar issues (e.g., combat trauma, military sexual trauma) to normalize their symptoms and reduce shame and stigma associated with their experiences, and group members may be able to challenge each other in ways a group leader cannot because of perceived shared status as trauma survivors. Group therapy instills hope by allowing group

members to see others at different stages in the treatment process. Group cohesiveness results in members of a group cohort gaining a sense of belonging and acceptance as they unite over a common treatment goal. In sum, group therapy can be effective for a wide range of mental health issues, professional clinical practice guidelines exist, and unique mechanistic qualities of group therapy have been identified through decades of research. Group therapy for PTSD is used widely in VA clinics because such interventions provide an opportunity for validation and support from peers, which is vital given the specificity of military-related trauma, and opportunities to learn from others' experiences [30, 31].

The National Center for PTSD and the Agency for Healthcare Research and Quality have created the PTSD Trials Standardized Data Repository (PTSD-Repository), a freely accessible database of >300 published randomized controlled clinical trials of PTSD treatment. A search of the PTSD-Repository reveals 32 different randomized controlled trials (RCT) of group-based interventions for PTSD between 1997 and 2018. A Pubmed search for "group psychotherapy" and "PTSD", filtering for "RCTs" and "2018-2020", led to two additional studies for a total of 34. Of these, 21 involved group therapy only, nine involved group-based complementary and integrative health interventions (e.g., yoga, music, nature), and four involved both.

Of the 25 studies involving group therapy, sample size ranged from 18 to 360 participants and 56% of the studies involved participants who were active military or veterans. The number of therapy sessions ranged from 2 to 35 and session length ranged from 1 to 6 hours. Active treatment arms included: nine studies of trauma-focused group cognitive-behavioral therapy [32-40], four studies looked at some form of group mindfulness-based therapy [41-44], three studies investigated trauma-focused group cognitive processing therapy [45-47], two studies investigated group memory specific training [48, 49], and the other seven studies each investigated a unique modality of experimental group therapy for PTSD [50-56]. The studies reviewed were heterogeneous in terms of target therapy, comparison condition, PTSD outcome measure, and trauma sample.

Fourteen studies compared one group intervention to another group intervention, seven compared a group intervention to a waitlist control, four compared a group intervention to individual minimal contact or treatment-as-usual. In comparison to group therapy, all 11 studies with a waitlist or treatment-as-usual control demonstrated a beneficial effect of group therapy [32-35, 37, 38, 49, 51, 53-55]. When different types of group therapy were compared, six studies demonstrated improvement of experimental trauma-focused group therapy over control group treatment [41-43, 46, 50, 56] and eight studies showed that both the experimental and control group treatments had significant reduction in symptoms and/or there was no significant difference in symptom reduction [35, 36, 39, 40, 44, 45, 48, 52]. In the largest group therapy RCT (n=360 veterans), there was no difference in symptom reduction between trauma-focused, exposure-based, group therapy and present-centered group therapy [39]; however, rates of drop out from treatment were higher for the trauma-focused treatment. Finally, Resick et al. (2017) demonstrated that improvement in PTSD severity was greater when cognitive processing therapy was administered individually compared with the group format; although, both modalities demonstrated significant reduction of PTSD symptoms, with no differences in remission or severity of PTSD at the 6-month follow-up [47]. Of note, these trials did not tend to include participants with comorbid disorders, such as substance use disorders, depression, or other anxiety disorders.

2.2.3 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by Merck pharmaceutical company in 1912 [57, 58]. MDMA binds to the monoamine transporters, enhancing synaptic

levels of serotonin and norepinephrine, and to a lesser extent dopamine, by vesicular carrier-mediated release and reuptake inhibition [59-65]. MDMA increases levels of affiliative neurohormones oxytocin and vasopressin, which are associated with increased trust and attenuation of reactivity to threatening cues, and cortisol and prolactin. The indirect effects of MDMA on central and peripheral neurohormone release contribute to a novel mechanism that may help regulate the HPA axis, impacting the core physiological pathology of PTSD, which may contribute to a durable remission.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to 2 hours after the initial dose. Effects of the initial dose last 3 to 6 hours, which is extended to 5 to 8 hours with a supplemental dose administered 1.5 to 2 hours post initial dose. Orally administered MDMA has a half-life of 7 to 9 hours in humans. Unlike approved PTSD medications, therapeutic effects of MDMA have a rapid onset, and do not require daily dosing or a steady state in the blood to be effective. Thus, the effects of MDMA are distinct from and work through different mechanisms than anxiolytics and SSRIs. Despite being a Schedule I controlled substance, there is no evidence that limited doses of MDMA in controlled clinical settings create a physical dependence or drug seeking behavior. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (unregulated material represented as containing MDMA) [66, 67]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [68] . Hence, MDMA is said to have low abuse potential in clinical settings.

A detailed description of the chemistry, pharmacology, efficacy, and safety of MDMA is provided in the Investigator's Brochure (IB).

2.2.4 MDMA-Assisted Therapy for PTSD

Many therapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in therapy with an appropriate level of emotional engagement [69]. To be effective, exposure must be accompanied by a degree of emotional engagement or "fear activation" while avoiding dissociation or overwhelming emotion [70]. This has been referred to as working within the "optimal arousal zone" or "window of tolerance" [71-73].

The combined neurobiological effects of MDMA increase compassion for self and others, reduce defenses and fear of emotional injury, and enhance communication and introspection. MDMA produces anxiolytic and prosocial effects, which counteract avoidance and hyperarousal in the context of therapy. PTSD increases amygdala activity, causing heightened encoding of fearful memories and decreases blood flow in the prefrontal cortex. In contrast, MDMA acutely decreases activity in the amygdala [74], and there is some indication that MDMA may increase activity in the prefrontal cortex (PFC) [75]. Another study showed increased functional connectivity between the amygdala and hippocampus, and decreased connectivity between the amygdala and PFC [76]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [74], compatible with its reported reduction in fear or defensiveness, and counteracts the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [77-79]. The reduction in stress-induced activation of the amygdala may be supported and enhanced by interacting with the therapy team during and after the MDMA experience. The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process. MDMA enhances perceived self-authenticity [80] and a naturalistic study suggests that it can increase self-compassion [81], effects that may support and contribute to the therapeutic process. MDMA is capable of inducing unique psychopharmacological effects, including decreased fear and increased wellbeing, sociability,

interpersonal trust, acceptance of self and others, and ability to address these issues without extreme disorientation or ego loss due to alert state of consciousness. These factors taken together can provide the opportunity for a corrective emotional experience.

A combined treatment of MDMA and therapy may be especially useful for treating PTSD because MDMA can attenuate the fear response of a perceived threat to one's emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [82-85]. Elimination of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to information about them [86]. Participants are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. In healthy controls, MDMA reduces reactivity to unpleasant memories [87]. MDMA seems to engender internal awareness that even painful feelings that arise are an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of the trauma as a past event, a more accurate perspective about its significance, and a heightened awareness of the support and safety that exists in the present. As a result, MDMA-assisted therapy may enable participants to restructure their intra-psychic realities and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

The therapeutic method is described in further detail in the Treatment Manual of MDMA-Assisted Therapy (Treatment Manual) [88], which the sites and therapy teams will be trained on prior to the study.

2.2.5 MDMA-Assisted Group Therapy for PTSD

Healing rituals conducted in a group context and involving the consumption of psychoactive substances leading to altered states have been commonplace among traditional cultures for millennia [89, 90]. In the United States, from approximately 1976 to 1985, MDMA was used as an adjunct to therapy, including group therapy [91-94], although published accounts were generally uncontrolled, proof-of-concept, case studies. This group MDMA work was modeled after indigenous healing ceremonies as well as the clinical work of Stan and Christina Grof [95, 96] and typically involved three therapists together with 8-15 patients with anxiety, depression, or "psychosomatic disorders". Wagner et al. (2019) also describe a recent successful protocol for couples therapy combining cognitive-behavioral conjoint therapy for PTSD and MDMA-assisted therapy [97]. No clinical trials adhering to modern-day scientific rigor have examined MDMA-assisted group therapy.

2.2.6 Previous Clinical Experience with MDMA

MDMA-assisted therapy is a novel treatment package that combines therapeutic techniques with the administration of MDMA as a pharmacological adjunct intended to enhance certain aspects of therapy. Chemists Shulgin and Nichols were the first to report on the effects of MDMA in humans [98], with 80 to 160 milligrams (mg) MDMA required to produce desired subjective effects in humans [98, 99]. MDMA was found to robustly influence human emotional status in a unique way [98] without adversely affecting physiological functions or perception, such as visual perception or cognition [100-103]. In the 1970s, therapists used MDMA-assisted therapy to treat psychological disorders, including anxiety, even though the drug had not been studied controlled clinical trials [104]. Legal therapeutic use continued until its placement on the U.S. Controlled Substances Act of Schedule 1 substances in 1985 [83, 86, 105]. An estimated 500,000 doses of MDMA were administered during therapy and personal growth sessions in North America prior to its scheduling [83, 106]. A few uncontrolled human studies of MDMA assessing safety in a controlled setting occurred in the 1980s [94, 107].

Controlled human studies for clinical development of MDMA commenced in the mid-1990s with a MAPS-funded investigator-initiated Phase 1 dose-response safety study [108, 109]. Starting in 2000 in Spain, MAPS funded a Phase 2 investigator-initiated dose-response effect and safety pilot study in participants with PTSD that was terminated early due to political pressure. This study enrolled six participants, with four receiving a single session of MDMA-assisted therapy without any safety concerns and with some PTSD symptom reduction [85]. These studies formed the basis of clinical experience with MDMA prior to studies subsequently conducted under a MAPS IND with the FDA.

MAPS initiated an international series of Phase 2 clinical trials to develop the medical use of MDMA-assisted therapy for patients with chronic, at least moderate PTSD (CAPS-4 score: 50+), with at least 6 months of symptoms. Intent-to-treat (ITT) analysis of primary efficacy and safety data from six MAPS-sponsored MDMA PTSD Phase 2 clinical trials worldwide (MP1, MP2, MP4, MP8, MP9, MP12) consisting of 107 blinded participants with chronic PTSD was completed in 2016 [110]. In these studies, PTSD, independent of cause, appears treatable with a two- to three-session treatment package of MDMA-assisted therapy, as assessed by difference in CAPS-4 severity scores from baseline to 1 to 2 months after the final experimental session. Large placebo-subtracted effect sizes (Cohen's d=0.9), initial indications of efficacy, and favorable safety outcomes led to the approval of MDMA for the treatment of PTSD as a Breakthrough Therapy Designation (BTD) by the FDA in 2017 for expedited drug development [111]. Improvements were durable at least 12 months after the last Experimental Session in 91 participants who received a therapeutically active dose of MDMA in these Phase 2 studies with 67% not meeting PTSD diagnostic criteria per CAPS-4 assessment [112].

MAPS completed a pivotal Phase 3 clinical trial (MAPP1) in 2020, further demonstrating the efficacy and safety of MDMA-assisted therapy for treatment of PTSD [113]. In this randomized, double-blind, placebo-controlled study, 90 participants with severe PTSD (CAPS-5 score: 35+ with at least 6 months of symptoms) were treated across 15 sites. Similar to Phase 2 results, PTSD symptoms were significantly attenuated by MDMA-assisted therapy. Manualized therapy in conjunction with MDMA (divided-doses of 80+40 mg or 120+60 mg MDMA HCl) was statistically superior for PTSD treatment in CAPS-5 severity scores from Baseline to 2 months after three blinded experimental sessions in comparison to therapy paired with an inactive placebo ($p<0.0001$). At the primary endpoint, 67% of participants in the MDMA group no longer met diagnostic criteria for PTSD, compared to 32% of the placebo group. Based on the successful completion of MAPP1, a confirmatory Phase 3 clinical trial (MAPP2) is currently underway encompassing a sample of participants with moderate to severe PTSD.

As of October 01, 2020, with 341 individuals exposed to MDMA in the sponsor's development program across various indications and at least 1,434 participants in MDMA research studies conducted without sponsor support (for a total of at least 1,775 individuals), the sponsor has observed an acceptable risk-benefit ratio for MDMA-assisted therapy.

A comprehensive review of MDMA research can be found in the IB supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of MDMA may be found in the IB, Informed Consent Form (ICF), and/or Development Safety Update Report (DSUR).

2.3.1 Risk Assessment

Potential risks, summaries, rationale, and mitigation strategy can be found in Table 4: Risk Assessments. For more information, see Investigator's Brochure, section 7.4 Risk Assessment and Mitigation.

Table 1: Risk Assessments

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk of IMP		
Cardiovascular and Cerebrovascular Events	MDMA transiently increases heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes typically last no more than 8 hours. Most people do not experience elevations in cardiovascular parameters that exceed those seen after moderate exercise. An examination of safety data drawn from Phase 2 and Phase 3 studies of MDMA-assisted therapy detected a dose-dependent increase in systolic BP and to a lesser extent diastolic BP. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.	• Participants with controlled hypertension will undergo additional cardiovascular screening assessments (e.g., cardiac stress testing and carotid ultrasound) to assess cardiac function and risk of cerebrovascular events, see Section 8.6.5 Additional Cardiac Screening. • Before and after IMP administration in Experimental Sessions, the therapy teams monitor vital signs. The therapy team should attend to clinical signs and symptoms of potential rare complications of the cardiovascular effects of MDMA, such as stroke or acute myocardial infarction during Experimental Sessions. In the unlikely event any such situation arise, study teams will seek immediate emergency medical attention.
Negative Psychological Impact	Psychological distress from MDMA could arise from the onset of MDMA effects until the last effects have dissipated, or even later. Anxiety or distress during the session may also occur. In addition, psychological distress could arise following an Experimental Session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided.	• MDMA is only administered as an adjunct to supportive psychotherapy. • Non-drug preparatory sessions will be conducted before experimental sessions. • At least two non-drug integrative sessions will be conducted after each experimental session. • Phone contact with participants will be arranged during the week following the experimental sessions.

Thermoregulatory Events	Epidemiological reports of Ecstasy (unregulated material represented as containing MDMA) use have documented cases of hyperthermia resulting in rhabdomyolysis. In MAPS-sponsored Phase 2 and Phase 3 studies, MDMA administered in a controlled setting can produce a slight increase in body temperature (up to approximately 1° C).	• During experimental sessions, ambient temperature should be kept at a comfortable level. If a participant's temperature rises more than 1° C or the participant states that they feel hot, attempts should be made to decrease body temperature and increase comfort by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the participant. • If body temperature rises more than 1.5° C above baseline despite these efforts, the site physician should be consulted.
Osmolarity Changes	Epidemiological reports of Ecstasy use indicate that combining Ecstasy with increased consumption of water and permissive factors, such as strenuous exercise in warm ambient temperatures, can cause in changes in osmolality resulting in hyponatremia.	• Participants will be limited to a maximum of 3 liters of fluid consumption during experimental sessions.
Reproductive and Developmental Risks	MDMA has been demonstrated to be negative for genotoxicity, both *in vitro* and *in vivo*, with and without metabolic activation. Consistent with this, despite very high doses of MDMA being tested in preclinical studies, none have reported carcinogenic effects. However, there is no clinical data on the use of MDMA in pregnant individuals.	• Urine pregnancy tests will be conducted during screening and immediately prior to any experimental session. • Participants who are able to become pregnant will be required to adhere to contraceptive measures with a <1% failure rate, as described in Appendix 2: Contraceptive and Barrier Guidance.
Abuse Potential	Despite its classification as a Schedule I drug (U.S.), there have been no AESIs reported and MAPS-sponsored Phase 2 and Phase 3 studies which could be suggestive of abuse potential among research participants treated with MDMA.	• MDMA is only administered under supervision and no take-home doses are administered. MDMA administration and handling follows all regulations pertaining to the use of controlled substances within research studies.

Risk of Study Protocol/Procedures		
Discomfort with Medical Assessments	Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress.	• Medical examinations and blood draws are required to establish eligibility for the study and cannot be omitted from the protocol.
Loss of Privacy Due to Video Recording of Sessions	Many of the visits with participants are required to be video recorded to ensure reliability between IR assessments and adherence to the Treatment Manual. Video recordings also enable clinical supervision of site therapists. Should these recordings be accessed by unauthorized individuals, there is a risk of loss of privacy. Because of the nature of the study (providing therapy) and need for supervision and adherence rating, there is no way to conceal the participant's physical appearance or personal health information relating to life events and trauma history.	Video procedures are designed to meet security standards that are expected of facilities providing medical care. Video Storage: • Video/audio recording occurs for telemedicine remote visits via Cisco WebEx, and, at in-person therapy sessions using the Valis Biosciences ACAM system. The ACAM system utilizes a secured iPad managed by Valis for clinical video recording that transmits the video to a secure web application, ValisR, after recording is complete. ValisR uses Amazon Web Services (AWS) for the secure storage of all video data. • Recordings of remote telemedicine visits captured via Cisco WebEx are stored on Cisco's servers, accessible only to WebEx system admins, until they are imported to ValisR. On successful transfer to ValisR, a delete request is submitted for the copy on Cisco's cloud storage. Encryption: • Video data captured by the ACAM system are encrypted on the device at the time the recording ends, in transit to AWS, and at rest while stored on AWS. If transfer from ACAM to AWS is not possible at the time the recording ends (for example due to networking outages), then the video is stored in encrypted form on the device until upload is available. • WebEx Meetings utilizes AES 265 encryption for media streams transferred over a TLS secured channel. WebEx recordings are encrypted both at the file level and at the logical volume level. The file key is a 256-bit AES-GCM key. This file key is then encrypted with a master key based on AES 256 that is rotated based on policy and saved to a hardware security module (HSM).

		Authorization: • Only WebEx and ValisR system admins have rights to video data management. Both WebEx and ValisR have robust audit logging for tracking video assignment and access. Data Transfer: • Video and audio data is transferred to either the ValisR app or the Cisco WebEx Cloud, depending on the capture method. Data captured by ACAM devices being sent to ValisR is transferred to AWS data centers. Data captured by Cisco WebEx Meetings is transferred to Cisco Cloud servers. All data is transferred electronically in encrypted form over TLS encrypted channels. Refer to Cisco's WebEx Meetings whitepaper for more information.
Discomfort related to Group Therapy	During both non-drug and MDMA-assisted therapy sessions, participants are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with therapy, the discomfort associated with therapy is unavoidable and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists. Participants may feel discomfort related to participating in therapy in a group setting, including discomfort with sharing personal experiences and emotions with a group, discomfort with interpersonal dynamics with another participant in the group, negative self-comparison to other group participants, or empathic distress associated with observing other group participants in the process of challenging experiences.	• Therapy teams support participants as they bring conscious awareness to difficult feelings, memories, or body sensations during the course of treatment. This is supported through empathic presence and establishment of a strong therapeutic alliance, a safe container, and a comfortable setting in which the therapeutic process takes place. • Therapy teams may also support participants through discomfort related to therapeutic processing of trauma through a variety of practices including, but not limited to, use of music, breathwork, and sensorimotor and somatic psychotherapy practices. • Therapy teams assess participants' support networks and help participants to consider ways in which their support system can be of help during the time between therapy sessions. • During MDMA-assisted therapy sessions, MDMA may catalyze therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences without being overwhelmed by anxiety or other painful emotions. Frequently, participants are able to experience and express fear, anger, and grief as part of the therapeutic process with less likelihood of either feeling overwhelmed by these emotions or of avoiding them by dissociation or emotional numbing. • At times, a participant may experience strong "negative" emotional reactions, including feelings of loss of control. When the therapists see that the participant's distress is interfering with their ability to stay focused on the inner experience, they intervene, encouraging the participant to stay present with deeper levels of emotion, including distressing feelings, and to trust that it is safe to face the experience. The empathic presence of the therapy team can support a participant

		to tolerate and titrate the discomfort of addressing challenging emotions and memories in service of healing. • Therapists are experienced in facilitating group therapy dynamics and in encouraging positive group effects while minimizing negative interpersonal group dynamics. • Cohorts will be carefully selected (see Section 5.6 Recruitment Strategies) according to individual factors expected to facilitate a sense of camaraderie and trust amongst participants. • Therapists will prepare participants for the possibility of negative self-comparison to other group participants, reminding them that each person's journey takes a different trajectory, and supporting participants to see the positive gains in their own healing process. • Participants will be asked to retain an inward-facing focus during the group MDMA session, with time for group discussion reserved for the beginning and end of the session; this will minimize the possibility of empathic distress. Therapists are experienced in supporting participants who are experiencing heightened emotional responses to others' challenges. If needed, therapists may bring a participant in a state of audible/visible distress to another study room so that other participants may remain engaged in their own internal experience.
Loss of Confidentiality due to group therapy	In group therapy, participants are asked to discuss their experiences, thoughts, and emotions with one another. There is a possibility of breach of confidentiality by another participant in the group.	• Explicit agreements are made by all participants at the start of study participation that they will hold what is said by other participants in the therapeutic process in confidence. • Confidentiality agreements are reinforced in each group therapy session.
Other		
Suicide and Risk of Self-Harm	Suicidal ideation and behavior are disease related events with high incidence in populations of people with PTSD, especially those suffering from chronic PTSD. Due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event in order to reprocess the memory in a new, therapeutic way, thoughts of ending one's life may surface during the process. In previous MAPS-sponsored clinical trials C-SSRS scores have escalated during the Preparatory Sessions,	• Should a participant be at serious risk to themselves, then the therapy team and site staff will intervene appropriately, consistent with professional practice standards. In extreme circumstances, this may involve summoning external crisis management teams for further assessment which may lead to involuntary hospitalization.

	which is thought to be a result of preparatory discussion of traumatic experiences, and/or participants concomitant tapering off long-prescribed medications, such as SSRIs and benzodiazepines. During both non-drug and MDMA-assisted therapy sessions, participants are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. Participants are also asked to report on their suicidality in these sessions and every other day over phone through C-SSRS administration. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with therapy, the distress associated with therapy is unavoidable and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.	
Inadequate pain management in participants using non-approved opioids	Certain long-acting opioid pain medications are not permitted during the study due to the potential QT-prolonging effects. The permitted opioid medications allowed in the study are listed in Section 6.8.2 Permitted Concomitant Medications. For some participants, the ability to achieve acceptable pain relief from the new opioid may not be possible.	• Participants requiring opioid pain medication may be cross-tapered to an approved opioid medication with an acceptable QT-prolongation profile.

2.3.2 Benefit Assessment

There is no guarantee that participants will benefit from taking part in this research study. Participant's symptoms of PTSD may improve while taking part in this study. Information obtained from this study may help doctors and researchers to improve treatment and treatment access for PTSD and other mental health conditions in the future.

2.3.3 Overall Benefit Risk Conclusion

Based on the previously reported data and the current state of scientific knowledge, MDMA-assisted therapy demonstrates significant benefit that outweigh the risks using a 2 or 3-session treatment model combined with non-drug therapy sessions for preparation and integration.

Across Phase 2 and Phase 3 studies, the overall rates of AEs and reactions are low and generally self-limiting. In addition, there was an absence of AEs supporting drug dependence, intentional drug misuse, and substance abuse, and one participant to date has reported experiencing hallucinations that reflect acute intoxication in PTSD patients in a controlled therapeutic setting. Proper preparation, testing, monitoring, and follow-up support is expected to mitigate the potential risk for cardiovascular events or psychologically distressing events that have been noted as medium-level safety risks. Risk mitigation mechanisms have been incorporated into the study design and will reduce the difficulties that participants might have with adverse reactions, as described in Table 4: Risk Assessments. This Phase 2 study is intended to assess the safety and efficacy of MDMA-assisted group therapy in the treatment of PTSD within a controlled clinical setting. Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with MDMA-assisted therapy are justified by the anticipated benefits that may be afforded to participants with PTSD.

3.0 Objectives and Endpoints

The overall objective of this study is to use standard clinical measures to explore the safety and feasibility of open-label MDMA-assisted therapy with a divided-dose of MDMA in the group therapy context in reducing PTSD symptomology in veterans.

4.0 Study Design

4.1 Overall Design

This Phase 2, open-label, non-randomized, 3-cohort study assesses the feasibility and safety of MDMA-assisted group therapy for the treatment of PTSD in veterans. The study will be conducted in up to N=18 participants, recruited in three cohorts of up to six participants and receive therapy sessions throughout their participation in these groups.
For each participant, the study will consist of:

- **Screening Period and Enrollment**: phone screen, informed consent, eligibility assessment, and enrollment of eligible participants.
- **Preparatory Period:** Preparatory Sessions, and baseline assessments.
- **Treatment Period**: two Experimental Sessions, and four Integrative Sessions following each Experimental Sessions.
- **Follow-up Period and Study Termination**: Primary Outcome assessment and Study Termination visit.

After the Screening Period and Enrollment, eligible participants will begin a ~4-week Preparatory Period. Participants will attend four, 90-minute, non-drug, Preparatory Sessions, including three group sessions and one individual session.. Following the Preparatory Period, participants will begin an ~8-week Treatment Period comprised of two Experimental Sessions, each followed by four Integrative Sessions.

MDMA will be administered twice during the Treatment Period: one Individual Session and one Group Session. The Experimental Sessions will last ~8 hours. Four 90-minute Integration Sessions, each one week apart, will follow the Individual Experimental Session. The first Integration Session will be Individual, occurring the morning following Experimental Session 1, and the other three will be Group Integration Sessions. Finally, four Group Integration Sessions, each a week apart, will follow the Group Experimental Session. Integrative Session 2.1 will take place the morning after Experimental Session 2. A study termination visit will be conducted at the end of the study.

4.2 Scientific Rationale for Study Design

PTSD is a chronic and disabling stress-related condition associated with serious adverse health outcomes and identifying novel treatments with durable effectiveness is timely and important. Military veterans are disproportionately affected by PTSD in comparison to the general population and group therapy is widely used in VA clinics to treat PTSD. This open-label study will evaluate the feasibility and safety of MDMA-assisted group therapy for the treatment of PTSD in veterans. The first Experimental session will be administered in an individual treatment session with two co-facilitators in order to familiarize each participant with the therapeutic experience. The second Experimental session will be administered in a group treatment session in which all cohort participants will simultaneously receive MDMA in the presence of four trained co-facilitators. The CAPS-5 is considered the international gold standard for the diagnosis of PTSD and the assessment of PTSD symptom severity. Safety data will be collected throughout. The data collected in this study will be analyzed both individually and by cohort.

Experimental Sessions, both Individual and Group, will primarily follow the treatment approach outlined in the Treatment Manual for individual participants. Previously reported studies using group sessions in MDMA studies will also inform the format of Group Experimental Sessions in this protocol. As part of the protocol development process, the team of MAPS-trained therapists will adapt the Treatment Manual in order to apply to a group therapy context.

4.3 Justification for Dose

Similar MDMA doses to those proposed in this study have been safely used in previous Phase 2 studies sponsored by MAPS. Phase 2 studies indicate that 63, 84, and 105 mg MDMA (equivalent to 75, 100, and 125 mg MDMA HCl) initial doses followed by a supplemental dose are active and effective at reducing PTSD symptomology following two to three Experimental Sessions. MDMA initial doses with an optimal risk-benefit ratio range from 63 mg dose (Cohen's d Independent Groups Pre-test Post-test [dIGPP]=2.73, N=7) to 125 mg dose (Cohen's dIGPP=0.77, N=58) of MDMA with a 2-session treatment package. In Phase 2 studies, the sponsor observed a 36.4 point mean decrease in CAPS-4 scores among active dose (63 to 105 mg MDMA, equivalent to 75 to 125 mg MDMA HCl) participants receiving two Experimental Sessions (N=72). Larger doses have been safely administered in MP2 (126 mg and 63 mg supplemental MDMA, equivalent to 150 mg and 75 mg MDMA HCl) and in Phase 1 studies (126 to 135 mg MDMA, equivalent to 150 mg and 160 mg MDMA HCl). The results of these Phase 2 studies led to the selection of 120 mg MDMA as the initial active doses.

This open-label study will examine the effects of a divided-dose of 134 mg to 150 mg of MDMA (equivalent to 160 mg to 180 mg MDMA HCl) administered in two Experimental Sessions. Participants will receive an initial dose of 100 mg and a supplemental dose of 34 mg or 50 mg MDMA (equivalent to 120 mg and a supplemental dose of 40 mg or 60 mg MDMA HCl) at 1.5-2 hours after initial ingestion, unless tolerability issues emerge with the initial dose or the participant declines, see Section 6.5 Dose Modification. Strength of supplemental dose will be the same for all participants and will be determined by drug supply availability at the start of the trial. The initial active dose is expected to produce all commonly reported effects of MDMA. The supplemental dose prolongs the subjective effects of MDMA without producing physiological effects much greater than peak effects occurring after the initial dose and will be administered unless there is a reason to withhold. Total amounts of MDMA to be administered per Experimental Session range from 100 mg to 150 mg (equivalent to 120 mg to 180 mg MDMA HCl).

Table 2: Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1 (Individual)	100 mg	34 or 50 mg	100 to 150 mg
2 (Group)	100 mg	34 or 50 mg	100 to 150 mg
		Total Cumulative Dose	200 to 300 mg

*Unless tolerability issues emerge with the initial dose or the participant declines.

Examples of tolerability issues may include: if a participant experiences a severe adverse event after administration of MDMA during an experimental session, or they experience clinical signs and symptoms that may suggest end organ effects as specified in the protocol, the supplemental dose may not be administered. Examples of these symptoms include chest pain, shortness of breath, neurological deficit or confusion, or other potential indicators of end organ effects that will prompt additional vital sign measurements, and intervention if appropriate. Please refer to Table 4: Risk Assessments for additional details.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if they have completed all periods of the study including the last visit.

The sponsor has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform participants and will ensure they receive appropriate therapy, follow-up, and plan moving forward. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with country regulations.

5.0 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Be 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Are a military veteran.
3. At Screening, meet DSM-5 criteria for current PTSD
4. Fluent in speaking and reading the predominantly used or recognized language of the study site.
5. Able to swallow pills.
6. Agree to have study visits video-recorded, including Experimental Sessions, IR assessments, and non-drug therapy sessions.
7. Able to identify appropriate support person(s) to stay with the participant on the evening of the Experimental Session, see Section 8.2.4 Support Person.
8. Able to provide a contact (relative, spouse, close friend, or other support person) who is willing and able to be reached by the investigators in the event of the participant becoming unwell or unreachable.
9. Agree to inform the investigators within 48 hours of any medical conditions and procedures.

Weight

10. Body weight of at least 48 kilograms (kg).

Sex and Contraceptive/Barrier Requirements

11. For participants assigned female sex at birth:
    - A participant is eligible to participate if not pregnant or breastfeeding, and one of the following conditions applies:
      - Is not able to become pregnant as defined in Appendix 2: Contraceptive and Barrier Guidance.

      OR
      - Is a person able to become pregnant (PABP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 2: Contraceptive and Barrier Guidance, during the study intervention period and for at least 10 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
    - A PABP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at study entry and prior to each experimental session.
    - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.

Informed Consent

12. Capable of giving signed informed consent as described in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have evidence or history of significant medical disorder

2. Have symptomatic liver disease
3. Have a marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds [ms] corrected by Bazett's formula)
4. Have a diagnosis of uncontrolled hypertension

Prior/Concurrent Clinical Study Experience

5. Current enrollment in any other clinical study involving an investigational study treatment or any other type of medical research, unless approved by the Medical Monitor.

Other Exclusions

6. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates participation in the study.
7. Previous participation in a MAPS-sponsored MDMA clinical trial.
8. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with study participation.

5.3 Lifestyle Considerations

All participants must agree to the following lifestyle modifications at time of signing the ICF and throughout the study.

Participants are eligible to enroll in the study if they:

- Are willing to complete all activities described in the ICF, which include MDMA dosing, therapy sessions, follow-up sessions, completing evaluation instruments, and all necessary telephone contact.
- Are willing to engage in group therapy sessions where there is a risk of a loss of confidentiality.
- Agree to not participate in any other interventional clinical trials during the duration of this study, without prior approval of the Medical Monitor.
- Agree not to take any new or prohibited medications or recreational drug substances during the course of the study without first discussing with the investigator in consultation with the Medical Monitor.
- Agree to not begin a new form of mental healthcare during the screening or treatment phases of the trial, without first discussing with the PI in consultation with the Medical Monitor.
    - It is acceptable for participants to continue ongoing mental healthcare, if it is not increased in frequency or specifically excluded by the study protocol.
    - All ongoing therapies should be documented by the site and discussed with the Medical Monitor prior to enrolment to avoid confounding treatment effects. In some instances, the Medical Monitor may request that the participant delay enrolment until their planned course of therapy is complete and an integration period has elapsed.

5.3.1 Leading up to the Experimental Session

- Agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each Experimental Session.
- Agree not to use caffeine or nicotine for 2 hours before each Experimental Session.

- Refrain from the use of any psychoactive medication not approved by the research team from Baseline through Study Termination.
- Are willing to comply with medication requirements per protocol (refer to Section 6.8 Concomitant Therapy). Medications will only be discontinued after enrollment per clinical judgment of the site physician in consultation with the prescribing physician.
- Are able to decrease dose of allowable opiates (per Sections 6.8.2 Permitted Concomitant Medications and 6.8.3 Prohibited Medications), if used for pain management, leading up to the Experimental Session in order to avoid taking the medication for at least 12 hours prior to the initial IMP administration and 24 hours after. During this period, the participant will be allowed to take the medication if needed for intolerable pain flare-ups.
- Agree that, for 5 half-lives plus 1 week preceding each Experimental Session to refrain from:
  - Taking any herbal supplement (except with prior approval of the research team).
  - Taking any nonprescription medications (except for non-steroidal anti-inflammatory medications or acetaminophen/paracetamol unless with prior approval of the research team).
  - Taking any prescription medications (with the exception of birth control pills, thyroid hormones, or other medications approved by the research team).

5.3.2 Post Experimental Session

- Are willing to be accompanied home after the Experimental Sessions either by the support person or escort, see Section 8.2.4 Support Person.
- Are willing to refrain from operating a vehicle for 24 hours following initial medication administration.

5.3.3 Meals and Dietary Restrictions

- Agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each Experimental Session.

5.3.4 Caffeine, Alcohol, and Tobacco

- Participants must agree not to use caffeine or nicotine (including nicotine patches) for 2 hours before and at least 6 hours after the initial dose during each Experimental Session.
- Prior to each dosing session, participants will abstain from alcohol for 24 hours before the planned start of dosing until after they leave the clinical site the following day.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Any participant who fails screening should be offered a referral to an outside therapist.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if approved by the investigator in consultation with the Medical Monitor. Rescreened

participants should be assigned a new screening number for every screening/rescreening event and should sign a new copy of the ICF.

5.4.1 Pre-Dosing Early Termination

'Pre-Dosing Early Terminations' are defined as participants who were deemed eligible and enrolled in the study at Enrollment Review but are deemed ineligible prior to the first Experimental Session, first IMP administration. These participants may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to the first Experimental Session, IMP administration. All enrolled participants, even Pre-Dosing Early Terminations, will be maintained in the Electronic Data System (EDC). Pre-Dosing Early Terminations are not considered evaluable.

Pre-Dosing Early Terminations may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the participant. At any time prior to first IMP administration, if a potential participant is deemed to be ineligible, classify as a Pre-Dosing Early Termination, notify the potential participant that they are not eligible for the study, and do not schedule additional assessments. Do not perform the next visit. Pre-Dosing Early Terminations will be provided a plan moving forward as described in Section 8.4.4 Plan Moving Forward.

5.5 Criteria for Temporarily Delaying

Due to the logistics of group therapy, there must be adequate flexibility factored into the timing of screening and enrollment. In order to construct a group cohort of six individuals, the study team must recruit and screen enough potentially eligible participants for a group cohort within a relatively short timeframe, consider appropriate distribution of individual factors during the group cohort selection process (as described in Section 5.6 Recruitment Strategies below), coordinate schedules among group members and participating staff members, and coordinate multiple medication taper plans and assessments. The timing of enrollment for individual participants may be delayed (e.g., to another group cohort that may better suit the individual) or adjusted at the investigator's discretion in order to achieve the same group start date (Preparatory Session 1) for the full cohort.

5.6 Recruitment Strategies

Recruitment efforts will focus on an enrollment target of six participants per group therapy cohort. Thus, study staff will need to concentrate enough screening assessments within a given enrollment period. Furthermore, group cohorts will be planned with considerations of veterans' service era (e.g., OEF/OIF, Vietnam), type of trauma (e.g., military-related trauma, combat-related, military sexual trauma), and gender identity to facilitate group cohesion. The optimal number and diversity of participants making up each group cohort will be flexible and adaptable and informed by earlier cohorts.

6.0 Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Medications

The Active Pharmaceutical Ingredient (API) to be used in this protocol is MDMA as a hydrochloride salt (HCl). Refer to the IB for a comprehensive review of the pharmacology, effects, and proposed mechanisms of action of the Investigational Medicinal Product (IMP).

Table 3: Study Medication Intervention Administered

Intervention Label	**Active Intervention**
Intervention Name	3,4-methylenedioxymethamphetamine (MDMA) as a hydrochloride salt (HCl)
Intervention Description	Initial doses per Experimental Session include 100 mg MDMA, followed 1.5 to 2 hours later by a supplemental dose of 34 or 50 mg MDMA (equivalent to 120 mg followed by 40 or 60 mg MDMA HCl).
Type	drug
Dose Formulation	capsule
Unit Dose Strength(s)	34 or 50 mg MDMA (equivalent to 40 or 60 mg MDMA HCl)
Dosage Level(s)	Initial: 100 mg MDMA (equivalent to 120 mg MDMA HCl) Supplemental: 34 mg or 50 mg MDMA (equivalent to 40 mg or 60 mg MDMA HCl)
Route of Administration	Oral
Use	Experimental
IMP and NIMP/AxMP.	IMP
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Each package will be an open-label container that will be used as bulk presentation at the study site and labeled as required per federal, state, and local regulations. This will include the following: *Caution: New Drug-Limited by Federal (or United States) law to investigational use.*

6.1.1.1 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study IMP received, and any discrepancies are reported and resolved before use of the study IMP.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the Pharmacy Manual.

6.2 Therapy

6.2.1 Description of Therapeutic Model

The largely non-directive therapeutic method of MDMA-assisted therapy is described in detail in the Treatment Manual. All therapy teams will be extensively trained through the MDMA Therapy Training Program prior to the study to ensure all participants are treated in a similar manner. The non-directive approach pertains to inviting inquiry and providing suggestion rather than directing the participant in the therapeutic approach. This requires active or engaged listening and responding, as well as facilitation of therapeutic action by providing support for approaching difficult material in a manner that does not interfere with the participant's spontaneous experience.

6.2.2 Implementation of a Therapeutic Model in a Group Setting

Each individual session (Individual Preparation, Experimental, and Integration Sessions) will be conducted according to the existing Treatment Manual with the same two-person therapy pair across sessions for each individual participant. Therapy pairs may be termed "co-facilitators" in this group protocol to reflect with standard group therapy terminology. Group Preparatory and Integration Sessions will be conducted by two co-facilitators and will incorporate a group therapy model. Four co-facilitators will be assigned to each group cohort of six participants. During the Group Experimental Session, all four co-facilitators will be present. Participants will be extensively prepared for the inner-directed approach to the Group Experimental Session. During the Group Experimental Session, participants will primarily be engaged in their own internal experience, interacting with their assigned facilitator(s) as needed; group processing will be reserved for before MDMA ingestion and toward the end of the session.

6.2.3 Therapy Team Qualifications

Therapy teams will be trained by the sponsor. Sites must ensure that the minimum requirements below are met:

- One or more two-person therapy pairs (co-facilitators), who have been reviewed and approved by the MDMA Therapy Training Program.
- One person per therapy team pair is required to be licensed to provide therapy according to state or province and local requirements.
- If one person on the therapy team is unlicensed, they will be required to have, at a minimum, a bachelor's degree and either be trained in mental health (including students in a postgraduate internship-type program providing detailed knowledge of mental health interventions and treatments) or have completed 1000 hours of behavioral health experience prior to co-facilitating sessions as a part of a co-pair.

A physician will be required to be on the study team to assess participant safety. Each site will also be required to have one person licensed to manage and administer controlled substances.

6.2.4 Therapy Training Program

The MDMA Therapy Training Program is designed to teach competency in applying the essential elements of this method of MDMA-assisted therapy. Therapy team members will receive specific training in the MDMA-assisted therapy method, protocol, and latest version of the IB. Training in the therapy method consists of reading the Treatment Manual, completing online training modules, and participating in an in-person or online training that includes watching and

discussing videos of Experimental Sessions. The required elements of the therapy are defined in the Treatment Manual, and teams will be trained on visit-specific sets of adherence criteria. In addition to this specific training, it is required that participating therapy team members have the proper background, education, and experience.

6.2.5 Adherence to Therapeutic Method

Therapy sessions, including Experimental Sessions, may be recorded, with recordings preserved for research and training purposes. Adherence ratings will be conducted by qualified, trained, and reliable adherence raters who will analyze video data from specific Preparatory Sessions, Experimental Sessions, and Integrative Sessions conducted with individual participants. The elements included in adherence criteria are specific to each type of session and are defined in the Adherence Manual. These ratings will be collected, at minimum, for each therapy team in the study. Ratings will be used to provide feedback to new therapy teams, to further characterize the manualized therapy, and for future exploratory research. In addition to adherence ratings of sessions conducted with individual participants, specific group-level Preparatory, Experimental, and Integrative sessions will be reviewed by Adherence Raters. As the adherence criteria for MDMA-assisted therapy for PTSD have been developed to identify adherence in sessions with an individual participant, Adherence Raters will qualitatively evaluate group sessions for adherence to the non-directive approach, providing written commentary identifying areas of accord or variation from the extant adherence criteria.

6.3 Measures to Minimize Bias

Participants, site staff, and the sponsor will be aware that each participant will be receiving open-label MDMA with no blinding at the site level. To minimize bias in measuring effectiveness, the sponsor will use an observer-blind, centralized, reliable IR pool to administer the Primary Outcome measure via tele-assessment. The IR Pool will have no knowledge of participant's study data or AEs and will only evaluate participants at Baseline and at the assessments scheduled after each Experimental Session. The IR Pool is blinded to study design, visit number, number of treatments, and any data from the treating therapy team after Baseline. IRs will be assigned to participants based on availability.

To ensure that all participants are treated in a similar manner, the site will be required to follow the protocol and Treatment Manual delineating minimum length of time per visit type and describing delivery of treatment. All Experimental Sessions are required to be at least 6 hours long. Adherence to the Treatment Manual will be checked by review of video by adherence raters. The sponsor will monitor data in real-time to ensure complete data collection for all participants, including those who discontinue treatment. Sites will be required to make and document a specific number of attempts to obtain follow-up data per protocol. All participants who receive at least one dose of IMP and complete at least one follow-up assessment will be included in the final mITT analysis.

Type of Study	
Open-label, no blinding at site level	This is an open-label study; potential bias will be reduced by the following steps: use of blinded, centralized, Independent Raters to assess baseline and outcome measure.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed at the site, they will receive study IMP directly from the investigator or designee. The date and time of each dose administered will be recorded in the source documents. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Dose Modification

In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the participant will be administered a supplemental dose unless tolerability issues emerge or the participant declines, in which case no supplemental dose will be administered.

6.6 Continued Access to Study Intervention after the End of the Study

After completion of the study, no further access to the study intervention (IMP or therapy) will be provided. Participants will work with their therapy team to identify future plans for therapy and support as described in Section 8.4.4 Plan Moving Forward.

6.7 Treatment of Dosing Errors

For this study, any dose of MDMA greater than intended dose of study intervention within a 24-hour time period will be documented as a dosing error.

In the event of a dosing error, the investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE.
- Document the quantity of the dosing error.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Psychiatric Medications

Psychiatric medications approved for treatment of PTSD, are under investigation for treatment of PTSD, or which are used off-label to treat symptoms of PTSD are not permitted during the trial and must be tapered during the Preparatory Period. If the participant is being treated with any such medication(s) at enrollment, the participant will be encouraged to discuss medication tapering with their outside treating physician and will be required to give the site physician permission to do so as well. The medications will then be tapered in an appropriate fashion to avoid withdrawal effects and discontinued at least five half-lives plus one additional week for stabilization before Baseline to avoid the possibility of any interaction.

The site physician will consult the prescribing physician to initiate medication tapering for participants, as they must refrain from taking psychiatric medications throughout the study, with some exceptions, see Section 6.8.2 Permitted Concomitant Medications. The prescribing physician's opinion about medication discontinuation should be documented in the participant's study record. Tapering will follow a time course appropriate for the medication based on its half-life, with Baseline scheduled to occur after complete washout (five half-lives plus at least 1 week for stabilization). If the health of the participant worsens after tapering, the participant will be withdrawn from the study and will be treated according to standard clinical practice. This will be recorded in the eCRF.

The therapy team will request information about any changes in medication at each contact. The site physician will be responsible for reviewing and confirming all medications collected during the study.

All medications, non-prescription and prescription, will be collected from Screening through 7 days after the last Experimental Session. From 7 days after the last Experimental Session through Study Termination, only prescription or non-prescription medications taken to treat AEs will be collected. Throughout the protocol, all medications used to treat AEs will be collected, and all changes including discontinuations or additions to medications will be collected. The study team will inquire and document all information about withdrawal and tapering of medications, concomitant medication, and medication adherence in the eCRF Concomitant Medications.

Participants may return to taking psychiatric medications and discontinue study-required contraception methods after the final Study Termination visit if necessary.

6.8.2 Permitted Concomitant Medications

The site physician may prescribe necessary and appropriate medications in accordance with local country regulations during the study to treat AEs that do not respond to other management outlined in the Treatment Manual.

All psychoactive medications, herbal supplements, non-prescription medications, and prescription medications must be reviewed by the Medical Monitor. Failure to comply with protocol requirements for concomitant medications may result in withdrawal from treatment, depending on the investigator and Medical Monitor judgment.

6.8.2.1 Acutely Prescribed Medications

Acutely prescribed medication may be considered necessary if the participant experiences severe, persisting emotional distress, anxiety, or insomnia that is not resolved via empathetic listening or

diaphragmatic breathing. The study site will supply acutely prescribed medication that will be obtained locally if prescribed by the site physician.

The name, dosage regimen, and date of the acutely prescribed medication administered will be recorded.

Although the use of acutely prescribed medications is allowable at any time during the study, the use should be delayed, if possible. The site physician and therapist should use their clinical judgement as to if/when it is clinically appropriate to intervene pharmacologically.

6.8.3 Prohibited Medications

To be enrolled in the study participants must:

- Be willing to comply with all medication requirements per protocol. Medications will only be discontinued after enrollment per clinical judgment of the site physician in consultation with the prescribing physician.

The research team should only approve medications that clearly would not be expected to have any interactions with MDMA.

7.0 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of the site or study as a whole is detailed in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant may remain in the study and continue with remaining individual sessions, but will not participate in any further group therapy sessions. If the investigator determines it is in the participant's best interest to completely withdraw from the study, an early discontinuation visit should be conducted..

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted..
- The participant will be permanently discontinued from the study intervention and the study at that time. The site team will provide the participant with a plan moving forward as described in Section 8.4.4 Plan Moving Forward.
- If a participant develops any Exclusion Criteria that, in the opinion of the Medical Monitor or Site, affects the safety of the participant, the participant will discontinue treatment in Experimental Sessions but may remain in the study for any individual associated non-drug Therapy and Integrative Sessions.
- If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- If a participant withdraws, cohort will continue with reduced size.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (e.g., 3 telephone calls or emails). In addition, site shall reach out to the contact person (relative, spouse, close friend, or other support person) provided by the participant. Finally, 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.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8.0 Study Assessments and Procedures

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in SoA.
- The Clinical Research Associate (CRA) should be notified of any delays or deviations to study procedures and Medical Monitor consulted if necessary. If there are delays of more than 7 days between visits or contact, the site should assess the need for additional telephone contact with the participant to ensure safety.

8.1 Screening Period

Prospective participants may be pre-screened by telephone to ascertain if they meet basic eligibility criteria. Data from potential participants who do not pass telephone screening will not be entered in the eCRF, but reason of ineligibility will be documented on the Screening Log.

All individuals who are pre-screened should be assigned a Screening Number and recorded on the Screening Log.

At any time during Screening, if a potential participant is deemed ineligible, they will be classified as a Screen Failure, notified that they are not eligible for the study, and not be scheduled for any additional Screening assessments. Participants who are eligible by pre-screening will be invited to undergo the informed consent process, either in-person or via telemedicine as permitted by local and study site regulations.

Site staff (preferably a member of the therapy team who would be treating this potential participant) or central screener will explain and obtain written (or electronic) informed consent using the IRB-approved ICF. Written consent must be obtained prior to performing any tests or evaluations for the study. The signature may be obtained using an electronic 21 CFR Part 11 compliant system due to COVID-19. Discussion about the ICF may take place over a telemedicine visit or at the first in-person visit. If a participant fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.

Screening may take place over multiple visits and will be completed in-person, via tele-assessment, or over the telephone. To allow for recruitment and scheduling of each group therapy cohort, there is flexibility in the timing window of the screening procedures permitted in the protocol, see Section 5.5 Criteria for Temporarily Delaying.

Medical records, if available, should be requested from the participant's general practitioner to ensure a comprehensive medical history has been obtained.

Table 4: Screening Period and Enrollment

Visit	Visit Description	Individual or Group	Visit Timing
Phone Screening	Phone calls	Individual	Prior to initial screening
Site Screening	In-person Visits & Labs	Individual	After Phone Screening
IR Screening	Initial IR Screening and Screening CAPS-5 (T0)	Individual	After initial eligibility met (may occur over 2 sessions)
Enrollment	Enrollment Review	Individual	~5 days (4 to 14 days) post IR Screening

8.1.1 Independent Rater Screening Assessment

If a participant meets initial eligibility during Screening, an IR will continue the eligibility assessment via tele-assessment after reviewing the results of the LEC-5 and SCID-5-SPQ. The IR interview may be recorded to assess reliability of ratings. If possible, the potential participant should be present at the study site during this assessment, in case the therapy team is needed for support. If a participant reports suicidal ideation during this assessment, the IR will contact the therapy team after the call and present any concerns. The therapy team will follow-up with the participant to ensure safety, provide support, recommend treatment, or schedule a visit to the study site.

- Using the results of the SCID-5-SPQ to guide the interview, the IR will perform the SCID-5-PD.
- The IR will also ask relevant questions from the DDIS to identify dissociative disorders and administer the Since Last Visit C-SSRS to determine suicidal risk.

- The IR will complete MINI interview.
- The IR will measure the CAPS-5 at screening (referred to as Screening CAPS-5 T0) to assess eligibility criteria.
- The IR screening may take place over 2 sessions.

The results from the CAPS-5, MINI, SCID-5-PD, DDIS, and C-SSRS will be provided to the therapy team at the site to review along with all other Screening information to determine eligibility. Items assessed by the IR at this visit will be confirmed in the Preparatory Period by clinical observation. If site staff deem the participant eligible, schedule Enrollment (Visit 0).

After the initial screening visits, the IRs will be blinded to visit number, number of treatments received and any study data for the participant. IR visits will be assigned based on availability.

8.1.2 Enrollment

In advance of Enrollment, the site team will review all notes from Screening visits, medical assessments, IR assessments, notes, discussions, medical records, and measures against eligibility criteria. If the participant is eligible, the participant will be notified of enrollment in person or via telephone/tele-assessment.

8.1.2.1 Enrollment Review

The site team will review the results of the IR visit to ensure that the participant continues to meet eligibility criteria, prior to CAPS-5 assessment, consulting with the Medical Monitor as required.

At Enrollment, the site team will confirm eligibility by reassessing specified eligibility criteria and ensuring that the participant continues to agree to all lifestyle modifications. If >3 weeks elapse from Enrollment Review (Enrollment) and the start of group therapy (Preparatory Session 1), confirm no clinically significant changes in health.

8.2 Preparatory Period

Medication tapering will be initiated following enrollment, in collaboration with the prescribing physician, as applicable. Participants will undergo four Preparatory Sessions lasting approximately 90 minutes with the therapy team prior to the first Experimental Session. Adherence criteria for Preparatory Sessions should be followed per the Treatment Manual. The Preparatory Period will last 3-4 weeks, depending on duration of medication tapering. There must be at least 48 hours between Preparatory Sessions. The minimum time to complete the Preparatory Period is 3 weeks. In these visits, the therapy team will work with the participant to prepare for MDMA-assisted therapy, begin building therapeutic alliance, and promote a safe set and setting for confronting trauma-related memories, emotions, and thoughts.

Table 5: Preparatory Sessions

Visit	Individual or Group	Visit Timing
Preparatory Session 1	Group	~1 week (3 to 14 days) after Enrollment
Preparatory Session 2	Group	~1 week (3 to 14 days) after Preparatory Session 1
Preparatory Session 3	Individual	After Preparatory Session 1, but before (Baseline); Preparatory Session 2 and Preparatory Session 3 order may differ; post Taper
Baseline CAPS-5 (T1)	Individual	After Preparatory Session 3, but before Preparatory Session 4
Preparatory Session 4	Group	~3 weeks (17 to 28 days) after Preparatory Session 1; 1 to 14 days before Experimental Session 1

8.2.1 Group Preparatory Sessions 1, 2, and 5

Group Preparatory Sessions during the Preparatory Period will focus on psychoeducation about PTSD, building safety for the therapeutic relationship, developing the therapeutic alliance, and preparing participants for the first Experimental Session. Telephone calls may be scheduled between visits if indicated for tapering, safety, or any further questions about medical history.

At each 90-minute Preparatory Session, the therapy team or other qualified site staff will:

- Inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements. Record AEs as described in Section 8.7: Adverse Events, Serious Adverse Events, and Other Safety Reporting.
- Inquire about concomitant medication use and adherence.
- Confirm that medication tapering is ongoing or complete, as appropriate.
- If medication tapering is ongoing at Preparatory Session 2, site team to schedule a phone call after tapering and stabilization are complete.
- Administer Since Last Visit C-SSRS to determine suicidal risk.
- Discuss goals and expectations for the Experimental Session, following standard procedures and techniques described in the Treatment Manual.

At any time during the Preparatory Period, if a potential participant is deemed to be ineligible, the site team will classify them as an Enrollment Confirmation Failure, notify the potential participant that they are unfortunately not eligible for the study, and not schedule additional assessments.

8.2.2 Individual Preparatory Session 3 and Safety Review

At Preparatory Session 3 and Safety Review, the site team will confirm the participant continues to be eligible for the study by reassessing specified safety criteria and ensuring that the participant continues to agree to all lifestyle modifications. This may require approval from the Medical Monitor for the initial participants until confidence is established. If any eligibility requirements are not met before or during Preparatory Session 3 and Safety Review, the participant will be considered a Pre-Dosing Early Termination.

For eligible participants at Preparatory Session 3 and Safety Review, the therapy team or other qualified site staff will:

- Complete the third 90-minute Preparatory Session with the purpose of confirming all enrollment is met and completing final preparation for the first Experimental Session.
- Inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements. Record AEs as described in Section 8.7: Adverse Events, Serious Adverse Events, and Other Safety Reporting.
- Inquire about concomitant medication use and adherence.
- Administer Since Last Visit C-SSRS to determine suicidal risk.
- Perform urine pregnancy test (for PAPB only).
- Perform urine drug test.
- Actively support participant in the completion of Baseline self-reported measures. Completion of measures does not need to be recorded.

8.2.3 Independent Rater Baseline Assessment

At Baseline, an IR will measure the baseline CAPS-5 (referred to as Baseline CAPS-5 T1) via tele-assessment. This visit may be recorded to video to establish inter-rater reliability. The IR will also administer the SDS and DSP-I at this time. The Baseline CAPS-5 score (T1) will be used for baseline comparison for statistical analyses but will not be used for eligibility determination.

8.2.4 Support Person

During the Screening and Preparatory Period, the participant will identify an appropriate support person to stay with the participant on the evening of the Experimental Session. Participants will be required to be escorted to and from the study site after Experimental Sessions. The support person is not required to be the same as the escort for the participant. There may be more than one support person(s), and they will be responsible for providing companionship as needed overnight and contacting the study team with any questions or concerns. Any support person spending the night with the participant will be required to meet a member of the therapy team in person, during the Preparatory Period or in advance of the appropriate Experimental Session in-person to be oriented to the role. An escort who is responsible only for transportation need not meet with the therapy team to perform that role. The participant will provide contact information for the appropriate support person(s) in advance of each Experimental Session.

8.2.4.1 Orienting the Support Person

The support person(s) will receive printed instructions, including contact information of the study physician, therapists, investigator, and Study Coordinator and what to do in the case of an emergency. The support person will not provide therapy to the participant. Minimal discussion is acceptable, but only if initiated by the participant. The support person should not interpret the participant's experience or act as therapist. The therapy pair will discuss this explicitly with the support person and include this information in the written instructions.

The main roles of the support person include:

- Ensuring the participant is safely transported to and from the study site as appropriate (may be completed by a separate support person or escort).

- Ensuring that the participant does not leave the overnight location without accompaniment and does not leave the participant alone at the overnight location. The participant may have privacy at the overnight site.
- Ensuring the participant has a comfortable place to sleep and discuss the plan for wakeup, breakfast, and travel time for the next day's Integrative Session.
- Seeing to the participant's needs for food and liquids, including providing dinner and breakfast in accordance with the participant's dietary preferences.
- Eating with the participant unless they ask to be left alone.
- Cleaning up after the participant, including doing the dishes and handling bedding.
- Keeping all participant information confidential.
- Supervising the participant to ensure they do not consume drugs or alcohol on the night of the Experimental Session and that phone/computer time is limited.
- Remaining sober throughout the entire overnight stay.
- Remaining available to participant's needs throughout the night, but may sleep if the participant is sleeping.

8.3 Treatment Period

During the Treatment Period, which occurs over a duration of 7-9 weeks (Experimental Session 1 to Integrative Session 2.4), participants will complete two treatments. Each treatment consists of an Experimental Session, followed the morning after by an Integrative Session, phone follow-ups every other day for 14 days, a second Integrative Session within 2 weeks, a third Integrative Session within 3 weeks, and a fourth Integrative Session within 4 weeks. The Experimental Sessions will be scheduled 3 to 5 weeks apart.

8.3.1 Experimental Sessions

There will be two open-label Experimental Sessions (Experimental Session 1 and 2). Procedures for MDMA-assisted therapy will remain the same across all sessions and all procedures regardless of dose received. Experimental Sessions must be at least 6 hours long, measured from 30 minutes prior to IMP administration. At both Experimental Sessions, a dose of 100 mg MDMA (equivalent to 120 mg MDMA HCl) will be administered followed by a supplemental dose of 34 mg or 50 mg MDMA (equivalent to 40 mg or 60 mg MDMA HCl) 1.5 to 2 hours after the initial dose, unless tolerability issues emerge with the first dose or the participant declines. Strength of supplemental dose will be the same for all participants and will be determined by drug supply availability at the start of the trial.

Table 6: Experimental Sessions

Visit	Individual or Group	Visit Timing
Experimental Session 1	Individual	1 to 14 days after Preparatory Session 4; up to 28 days after Baseline CAPS
Experimental Session 2	Group	~4 weeks (21 to 35 days) after Experimental Session 1

8.3.1.1 Pre-IMP administration

- On the day of the Experimental Session, the participants will arrive approximately 30 to 60 minutes prior to IMP administration.

- The site team will ensure the participant has not used caffeine or nicotine 2 hours prior and fasted for 10 hours prior to IMP administration and agrees to comply with all other requirements per Section 5.3 Lifestyle Considerations.
- The site team will inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements and record AEs, as described in Section 8.7.5 Method of Detecting AEs and SAEs.
- The site team will complete symptom-directed physical exam, urine drug screen, pregnancy test (for PABP only), and concomitant medication review.
    - A positive drug screen will be reviewed by the site physician and may be cause for delaying IMP administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study, based on Medical Monitor review.
    - A positive pregnancy screen is cause for withdrawal from the protocol.
- The therapy team will administer Since Last Visit C-SSRS.
- The therapy team will review procedures for the Experimental Session with the participant and discuss the participant's goals, intentions, and concerns and some of the commonly experienced effects of MDMA.
- During the Group Experimental Session, all four co-facilitators will be present.
- Baseline blood pressure, body temperature, and pulse will be measured just prior to administration of the initial dose.
- A symptom-directed physical examination, or additional vital signs measurements, may be conducted at any time if clinically indicated.

8.3.1.2 During the Experimental Session

- After video recording has begun, a qualified staff member will administer the initial dose of IMP with water. The participant will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided for the participant if they wish to use them. Whenever they wish, participants may speak to the therapy team, who will provide guidance and support, as needed.
- During the Individual Experimental Session, after the first hour, if the participant has not spoken spontaneously, the therapy team will check in with them about the nature of the experience. For the rest of the experience, as appropriate, the therapy team will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging, as described in the Treatment Manual.
- During the Group Experimental Session, participants will primarily be engaged in their own internal experience, interacting with their assigned facilitator(s) as needed; group processing will be reserved for before MDMA ingestion and toward the end of the session.
- Fluids will be provided throughout the session but not to exceed three liters overall.
- Blood pressure, body temperature, and pulse will be measured approximately 1.5 to 2 hours after the initial dose, before the supplemental dose is administered.
- The site physician (if not part of the therapy team) will provide escalation criteria individualized to the participant to determine if the team site physician should be contacted.
    - If escalation criteria are met, a member of the therapy team will contact the site physician with a brief description of how the session is progressing and the recent vital signs to determine if the supplemental dose should be withheld.
    - If medical attention is needed, the site physician will provide further instruction or consult the Medical Monitor.

- A supplemental dose will be administered with a glass of water approximately 1.5 to 2 hours after the initial dose, unless the participant experiences tolerability issues.
- Food will be provided during the latter part of the session.

8.3.1.3 End of Experimental Session

- The therapy team will administer Since Last Visit C-SSRS.
- The therapy team will record AEs and concomitant medications.
- Blood pressure, body temperature, and pulse will be measured including a symptom-directed physical exam if clinically indicated.
- Participants may be dismissed if all medical and psychiatric parameters are acceptable, vital signs are stable, the participant is alert, ambulatory, and emotionally stable, and the support person or escort has arrived. If it is in the best interest of a participant for them to spend the night at the study site or nearby accommodations, the therapists will ensure an appropriate stay is provided.
- Each participant will be escorted home by either the support person or escort via car, rideshare, or public transportation and will not remain overnight at the study site.
- Each participant will stay with an identified appropriate support person on the evening of the Experimental Sessions, see Section 8.2.4 Support Person.
- Each participant will be instructed to call a member of the therapy pair when they arrive where they will stay for the night. If the therapy pair has not received a call within 2 hours after the participant has left the site, the therapists will call the participant and support person to confirm arrival.
- The therapy pair will ask about the participant's emotional well-being and invite them to begin the process of integration through self-reflection, journaling, meditation, or other quiet activities. The therapy pair will remind the participants that this evening should be an opportunity to rest and integrate and that they should avoid unnecessary stresses, chores, etc.
- The therapy team or site physician shall remain available to participants via 24-hour cellular phone for integration, as needed.

8.3.2 Telephone Contact After Experimental Sessions

A member of the therapy team will follow-up with the participant by telephone every other day for 14 days after each Experimental Session. Calls will not be made if there is an Integration Session scheduled the same day.

The goal of the telephone contact is to assess health changes, ensure participant safety, and offer support. Each call will last on average 5 to 15 minutes but could be longer to address participant concerns and to adequately assess wellbeing. Additional telephone contact can be initiated at the request of the therapy team or participant.

At each telephone contact, the therapy team will:

- Inquire about any possible changes in health, assess the participant's mental health and the status of any previously recorded AEs, and record AEs as described in Section 8.7: Adverse Events, Serious Adverse Events, and Other Safety Reporting.
- Inquire about concomitant medication use and compliance.
- Offer support in accordance with the Treatment Manual.
- Administer the Since Last Visit C-SSRS.

8.3.3 Integrative Sessions

After each Experimental Session, four Integrative Sessions will take place. Each session will consist of 90 minutes of therapy.

On the morning after the Experimental Session, the participants will be escorted to the study site via car, rideshare, or public transportation, as participants are not allowed to drive within 24 hours of administration of MDMA.

In addition to completing the study procedures, the therapy team will discuss and review events that occurred with the participant during the Experimental Session, including thoughts, feelings, and memories. If necessary, the therapy team will help the participants to reduce any residual psychological distress they are experiencing. The therapy teams will also encourage the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in Experimental Sessions to emotionally threatening everyday situations. The therapy teams will be supportive, validate the experience, and facilitate understanding and emotional clearing.

Table 7: Integration Sessions after Experimental Sessions

Following First Experimental Session		
Visit	**Individual or Group**	**Visit Timing**
Integration Session 1.1	Individual	Morning after Experimental Session 1
Integration Session 1.2	Group	~1 week (3-14 days) after Experimental Session 1
Integration Session 1.3	Group	~2 weeks (10-21 days) after Experimental Session 1
Integration Session 1.3	Group	~3 weeks (17-28 days) after Experimental Session 1; 1-7 days before Experimental Session 2
Following Second Experimental Session		
Integration Session 2.1	Group	Morning after Experimental Session 2
Integration Session 2.2	Group	~1 week (3-14 days) after Experimental Session 2
Integration Session 2.3	Group	~2 weeks (10-21 days) after Experimental Session 2
Integration Session 2.4	Group	~3 weeks (17-28 days) after Experimental Session 2

8.4 Follow-up Period and Study Termination

During the Follow-up Period and Study Termination, participants will complete a final CAPS-5 assessment and attend a Study Termination visit.

Table 8: Primary Outcome and Study Termination

Visit	**Individual or Group**	**Visit Timing**
Primary Outcome	Individual	after Experimental Session 2
Study Termination	Individual	after Outcome

8.4.1 Follow-up Period

After the final Integrative Session 2.4, participants will enter follow-up for approximately 4 weeks (+/-2 weeks) with no protocol required visits until the final Outcome assessment followed by a Study Termination. Participants will have access to therapy teams for support if needed, and additional visits via telephone, tele-assessment, or in person can be scheduled if requested. Participants will continue to comply with protocol requirements for concomitant medications until after Study Termination.

8.4.2 Independent Rater Final Assessment

Participants will have a final Outcome assessment at the completion of the follow-up period. An IR will conduct the assessments via tele-assessment. These assessments may be recorded to establish inter-rater reliability. The results may be shared with site staff during supervision by the therapy training team. Participants who have withdrawn from treatment will also complete a final

Outcome assessment immediately upon withdrawal. The IR will also administer the SDS and DSP-I.

8.4.3 Study Termination

Study Termination will take place 1 week (0-9 days) after the final CAPS-5 assessment and can occur on the same day as Outcome visit. Participants who have withdrawn from treatment but have continued for follow-up will also complete this assessment immediately upon withdrawal.

After all Study Termination measures and assessments are completed, the participant is considered terminated from the study. The participant can resume normal everyday life. The study team will provide a plan moving forward, which may include a referral for additional medical or therapeutic care, as described in Section 8.4.4 Plan Moving Forward. Eligible participants may be invited to participate in a future long-term follow-up (LTFU) extension study, which will be conducted under a separate protocol.

8.4.4 Plan for Moving Forward

At Study Termination, participants will be provided with a plan for moving forward. This plan will summarize treatments completed, current medications, and contact information for more information about the study if needed. Participants may request a referral for further therapeutic or medical care if appropriate. Enrolled participants who terminate the study early will be provided a plan for moving forward at their last contact. Screen Failures will be provided a referral if requested.

8.5 Eligibility and Efficacy Assessments

8.5.1 Primary Outcome Measure and Reliability

8.5.1.1 Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The CAPS-5 is a semi-structured interview that assesses index history of DSM-5-defined traumatic event exposure [114], including the most distressing event, time since exposure, to produce a diagnostic score (presence vs. absence) and a PTSD Total Severity score [114]. The CAPS-5 rates intrusion symptoms (intrusive thoughts or memories), avoidance, cognitive and mood symptoms, arousal and reactivity symptoms, duration and degree of distress and dissociation. The total severity score is a sum of symptom frequency and intensity scores for the subscales B (re-experiencing), C (avoidance) and D (hypervigilance) and ranges from 0 to 136, with higher scores indicating greater severity of PTSD symptoms. The CAPS-5 takes approximately 90 minutes to complete.

Assessment and Reliability of CAPS-5

The CAPS-5 will be administered by a blinded IR via tele-assessment. Interviews will be conducted by the centralized remote IR pool to enhance quality control by reducing site-level variation in interview fidelity and quality. The IRs will be trained and supervised by a research reliable trainer and will be supervised by qualified personnel. Interviews may be recorded in as many instances as necessary to establish reliability of a random selection of interviews for accuracy.

Per the CAPS-5 Training Manual for the IR Pool, IRs will ensure that every single item-level score is collected in every CAPS-5 interview. The CAPS-5 is administered by the IR in a neutral, non-leading manner to minimize the chance for bias. Avoiding a biased administration can be achieved by adhering to administration guidelines verbatim and only deviating from the script to clarify, re-direct, or query further if behavioral examples are needed to determine the appropriate symptom intensity rating. Avoiding building therapeutic/clinical rapport beyond the basic level of rapport needed to conduct the interview in the research setting also minimizes the chance for bias. Remote assessment assures that the rater who is collecting the Primary Outcome will not witness Experimental Sessions and the acute effects of IMP. Interviews may be recorded in as many instances as necessary to establish reliability of a random selection of interviews for accuracy. After the initial screening visit, the IRs will be blinded to visit number, number of treatments received, and any study data for the participant. IR visits will be assigned based on availability.

8.5.2 Secondary Outcome Measure

8.5.2.1 Sheehan Disability Scale (SDS) for PTSD for MAPS

The SDS is a 5-item measure of functional impairment [115]. The items indicate degree of impairment in the domains of work/school, social life, and home life, with response options based on a 10-point scale (0=not at all to 10=extremely), and five verbal tags (not at all, mildly, moderately, markedly, extremely). The SDS has high internal consistency and accurately identified 80% of a sample of primary care patients with mental disorders [116]. The Customized version of the SDS for PTSD for MAPS was developed utilizing the standard SDS. The first three items indicate degree of impairment in the domains of work/school, social life, and home life, with response options based on a 10-point scale (0=not at all to 10=extremely), and five verbal tags (not at all, mildly, moderately, markedly, extremely). The remaining two items assess Days Lost and Days Unproductive during the reporting period. The SDS for PTSD for MAPS maintains the same scale conventions as the standard SDS. To limit missing data, the summary measure used to analyze the treatment effect on SDS is the mean of the 3 item responses at each visit. Any participant who did not work during the reporting period due to reasons related to PTSD is scored as maximal work-related impairment on item 1. Any participant who did not work during the reporting period due to reasons not related to PTSD reports on the reason for not working and Item 1 is skipped. The SDS for PTSD for MAPS has been approved by Dr. David Sheehan for use in MAPS Research and is referred to throughout the protocol as SDS. The SDS for PTSD for the MAPS takes approximately 5 minutes to complete.

To limit missing data and ensure standardized administration, the SDS for PTSD for MAPS will be administered in a clinician-rated format by the centralized IR Pool via Teleassessment.

8.5.3 Screening Measures and Reliability

8.5.3.1 Mini-International Neuropsychiatric Interview (MINI)

This version of the MINI (7.0.2), a structured interview that was first developed in 1998 to be compatible with DSM and International Classification of Disease (ICD) criteria for psychiatric illnesses [117]. It is now compatible with DSM-5 and will be administered to screen for all major psychiatric conditions other than personality disorders. Each module of the MINI consists of two or three questions where the answer is either “Yes” or “No,” and decision-tree logic is used to determine whether to ask additional questions [118]. MINI items were highly reliable (interrater reliability between kappa of 0.8 and 0.99, test-retest reliability between 0.6 and 0.9 for all scales save “current mania”), and diagnosis via MINI was comparable to that made with the Composite

Diagnostic Interview and the SCID [119, 120] Testing on non-psychiatric samples did not create false positives [117]. The MINI takes approximately 90 minutes to complete.

To limit missing data and ensure standardized administration, the MINI will be administered in a clinician-rated format by the centralized IR Pool via Tele-assessment.

8.5.3.2 Structured Clinical Interview for DSM-5 for Personality Disorders: Self-report Questionnaire (SCID-5-SPQ)

The SCID-5-SPQ is a brief questionnaire designed as a self-report screening tool used to assess for personality disorders [121]. Potential personality disorders that satisfy diagnostic thresholds will be further assessed via clinical interview during the SCID-5-PD, see below. The SCID-5-SPQ takes approximately 20 minutes to complete.

8.5.3.3 Structured Clinical Interview for DSM-5 for Personality Disorders (SCID-5-PD)

The SCID-5-PD is a semi-structured diagnostic interview that assesses the 10 personality disorders of the DSM-5 [121]. The clinical interview is informed by answers on the self-reported questionnaire (SCID-5-SPQ). The SCID-5-PD takes approximately 60 minutes to complete.

To limit missing data and ensure standardized administration, the SCID-5-PD will be administered in a clinician-rated format by the centralized IR Pool via Tele-assessment.

8.5.3.4 Life Events Checklist for DSM-5 (LEC-5)

The LEC-5 is a 17-item self-report instrument designed to determine the presence of traumatic life events in the assessment and diagnosis of PTSD. It is a companion measure to the PCL-5 and will be used to assess PTSD. The participant indicates whether each event listed has occurred during their lifetime, permitting the possibility of marking multiple events [122]. The LEC-5 takes approximately 5 minutes to complete.

8.5.3.5 PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms, derived from the symptoms of PTSD per DSM-5 [123]. Participants indicate how much distress they have experienced due to symptoms such as "Repeated, disturbing memories, thoughts, or images of a stressful experience from the past," "Trouble remembering important parts of a stressful experience from the past," and "Feeling irritable or having angry outbursts" on a 5-point Likert-type scale (1=Not at all to 5=Extremely). The PCL-5 takes approximately 8 minutes to complete.

8.5.3.6 Dissociative Disorders Interview Schedule for DSM-5 (DDIS)

Questions on the DDIS specifically addressing dissociative disorder symptoms will be administered by a blinded IR via telemedicine. These questions are part of an intensive interview that includes questions concerning somatic and psychiatric symptoms. The interview is intended to assess and potentially distinguish between dissociative disorders and other disorders and between Dissociative Identity Disorder (DID) and a dissociative disorder not otherwise specified [124]. Owing to overlap with items found between the DDIS and other screening measures, only questions specifically addressing DID (items 117 to 132) will be assessed. The DDIS takes approximately 5 minutes to complete.

To limit missing data and ensure standardized administration, the DDIS will be administered in a clinician-rated format by the centralized IR Pool via Tele-assessment.

8.5.4 Exploratory Measures

8.5.4.1 DSP-I (The Dissociative Subtype of PTSD Interview)

The DSP-I is a clinician-administered interview designed by an international team of PTSD researchers to detect and assess severity of the dissociative type of PTSD [125]. It is recommended for use as an additional or complementary measure ("add-on") to the CAPS-5. Assessments of military veterans and civilians support the existence of a dissociative subtype of PTSD that is associated with PTSD severity and derealization and depersonalization [126-128]. It consists of two parts, but only Part 1 will be administered. Part 1 contains five items addressing depersonalization, four items addressing derealization, and a section that is administered if dissociative episodes are endorsed that assesses duration and perceived cause of episodes (seven items) and observer items (three items) addressing interviewee demeanor, including evidence of dissociation, such as forgetfulness or giving a statement that is bizarre within the context of the interview. If two or more items within this section are endorsed, this indicates the presence of other dissociative symptoms beyond depersonalization and derealization. The DSP-I takes approximately 15 minutes to complete.

To limit missing data and ensure standardized administration, the DSP-I will be administered in a clinician-rated format by the centralized IR Pool via Tele-assessment.

8.5.4.2 Adverse Childhood Experience Questionnaire (ACE)

The ACE is a 10-item checklist measure assessing number and types of adverse childhood experiences, including neglect and emotional, physical, and sexual abuse. The measure was first used in the context of a study investigating the relationship between childhood adverse experiences and health outcomes in adulthood [129]. Respondents are asked if an experience happened "often" and if so, to write "1". The total score reflects the number of adverse childhood experiences. Number of frequent adverse childhood experiences is associated with adverse health outcomes in adulthood, including greater likelihood of heart disease, chronic pain, and poor work performance [130-133]. The scoring method has been used in archival research, finding an association between increased scores and health problems in several generations [132]. In addition, developmental trauma events (DTE) during childhood and adolescence, including description and frequency of the events will be evaluated at screening and throughout the trial. The ACE takes approximately 4 minutes to complete.

8.5.4.3 Group Questionnaire (GQ)

The GQ is a 30-item self-report measure of the quality of the therapeutic relationships in a group setting. The GQ is empirically validated and sensitive to group level processes [134] with acceptable correlations with the Working Alliance Inventory, the standard measure of therapeutic alliance in individual therapy [135]. Subscales assess Positive Bonding (13 items), Positive Work (8 items), and Negative Relationships (9 items) organized within three structural dimensions: member-member, member-group, and member-leader relationships. Questions are rated on a 7-point Likert-type scale, 1 (not true at all) to 7 (very true). The measure yields a score for each of the three subscales, which have good internal consistency [134-136]. The GQ takes approximately 10 minutes to complete.

8.5.4.4 Beck Depression Inventory II (BDI-II)

The BDI-II is a revision of the BDI, a 21-item self-report measure [137, 138] that will serve as a measure of depression symptom severity [139]. The BDI-II has been validated, has high internal consistency and good test/re-test reliability, and is not overly sensitive to daily variations in mood [139]. Score cutoffs indicate: 0 to 13 minimal depression, 14 to 19 mild depression, 20 to 28 moderate depression, and 29 to 63 severe depression. Initial and subsequent studies report that the BDI-II total score has a reliability coefficient of 0.90 to 0.91 which is related to other measures of depression symptoms [140, 141]. The BDI-II takes approximately 10 minutes to complete.

8.5.4.5 Experiences in Close Relationships-Short Form (ECR-S)

The ECR-S is a 12-item self-report measure of the construct of adult attachment, resulting in scores for two factors: attachment anxiety and attachment avoidance. Questions are rated on a 7-point Likert-type scale. For this study, the term “romantic” will be substituted for “intimate,” defined as “emotional closeness, including close family relationships and/or romantic relationships”. Brennan et al. (1998) reported that the ECR long version had a high level of internal consistency within the two factors, with coefficient alphas of 0.91 and 0.94 for the Anxiety and Avoidance subscales, respectively [142]. This was confirmed for the short version of the scale with coefficient alphas of 0.78 (Anxiety) and 0.84 (Avoidance) [143]. Correlations between the Anxiety and Avoidance subscales were low (r=0.19), which indicates that these two subscales reflect distinct dimensions of attachment. The ECR-S also possesses good test-retest reliability and construct validity. The ECR-S takes approximately 5 minutes to complete.

8.5.4.6 Posttraumatic Growth Inventory (PTGI)

The PTGI is a 21-item scale assessing positive outcomes following trauma. The scale includes factors of New Possibilities, Relating to Others, Personal Strength, Spiritual Change, and Appreciation of Life. The PTGI is modestly associated with personality traits of optimism and extraversion. The scale has been used to assess how individuals have reconstructed or strengthened their perceptions of self, others, and the meaning of events in the aftermath of trauma [144]. The PTGI takes approximately 5 minutes to complete.

8.5.4.7 Cornell Services Index (CSI)

The CSI was developed to document the quantity and type of services used by adults seeking mental health treatment in Westchester County, New York, as part of an NIMH-funded study. Among the virtues of this instrument are its inclusion of all types of services (except pharmacy) while including a special focus on mental health services and ease of administration and portability. The CSI Guidelines for Administration and Scoring provides instructions on how a

trained interviewer would elicit accurate information to complete the form. Raters are taught to help interviewees establish the reference period by using holidays or personal events to define the assessment period. The validated assessment period is 3 months. The CSI's interrater and test reliability were evaluated in a sampled of 40 adults who sought mental health treatment [145]. Interclass correlation coefficient for all service types was 0.98, and test-retest reliability ranged from 0.54 to 1.00 which was deemed moderate to high. This protocol will utilize a modified version of the CSI in which all services are recalled for 6 months to balance the accuracy of self-report for outpatient visits and inpatient stays. This reference window would also better allow a pre-study/post-study comparison with the schedule of assessments because having more time for health service utilization would improve the duration over which we can expect to capture both outpatient and inpatient health services. The likelihood of detecting a relatively rare event of going to the hospital is greater over a 6-month period vs. a 3-month period. The CSI takes approximately 3 minutes to complete.

8.5.4.8 Social Provisions Scale (SPS)

The SPS a 24-item measure of the degree to which respondents' social relationships provide various dimensions of support [146]. The scale includes six subscales based on Weiss's (1974) social provisions theory: reliable alliance, attachment, nurturance, social integration, reassurance of worth, and guidance [147]. Each subscale has four items, two positively worded items and two negatively worded items assessing the absence of support. Questions are rated on a 4-point Likert-type scale with anchors of 1 (strongly disagree) and 4 (strongly agree). Cronbach's alpha coefficients of the six factors ranged from 0.67 to 0.76, and construct validity is supported. High correlation between the SPS and other measures of support provided evidence for the construct validity of the scale. The SPS takes approximately 5 minutes to complete.

8.5.4.9 Self-Compassion Scale (SCS)

The SCS is a 26-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion and recognizing one's own flaws and suffering as part of common human experience [148]. Respondents complete the SCS by indicating how typical they feel on each item on a 5-point Likert scale (1=Almost never and 5=Almost always). The scale has six sub-scales: Self-Kindness, Self-Judgment, Common Humanity, Isolation, Mindfulness, and Over-Identified. The mean of subscale scores serves as a total score. Analysis of SCS response indicated that subscales are all related to a higher order factor of self-compassion, and the measure has high test-test reliability at a level of 0.93. Neff *et al.* reported an inverse relationship between SCS total scores and scores on measures of depression and anxiety. Self-compassion and global self-esteem are both related to positive mood and optimism, but self-compassion may be more strongly associated with stable mood and less associated with self-rumination and anger [149]. The SCS takes approximately 6 minutes to complete.

8.5.4.10 EuroQol Five Dimensions – Five Levels Questionnaire (EQ-5D-5L)

The EQ-5D-5L is a two-part self-report questionnaire assessing health status. It consists of five dimensions; mobility, self-care, usual activities, pain-discomfort and anxiety-depression, and one visual analog scale (VAS). Responses are made on each dimension by checking one of five statement that best reflects their health on the day of measure completion, from the healthiest or fewest problems (e.g., "I have no trouble walking about") to the most trouble (e.g., "I am unable to walk about") [150, 151]. In the second part of the EQ-5D-5L, current degree of health ("your health today") is indicated by marking a 100 mm line, with 100 considered "the best health you can imagine" and one "the worst health you can imagine". The EQ-5D-5L does not sum

responses but treats each response on a dimension as a scale score, and the VAS (Visual Analogue Scale) is the location of the mark. The scale can permit comparison across groups on health profiles, and an index can be derived from matching the five-dimension scores and the VAS response with nation-specific datasets and calculator software or statistical software syntax designed for the measure. The EQ-5D-5L began as part of the EuroQoL measure, published in 1990 [152]. The instrument has been validated in populations from eight countries. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation [153]. The EQ-5D-5L takes approximately 3 minutes to complete.

8.5.4.11 Health and Work Performance Questionnaire Short Form (HPQSF)

The HPQSF is a short form of a larger measure of health and work performance that has selected items referring to absenteeism and work performance (Kessler, Ames et al. 2004). The larger measure was created by the WHO as part of the Global Burden of Disease initiative. It consists of eight questions selected from the larger Health and Work Performance Questionnaire, with one question containing five additional items. Items include questions concerning hours worked during an average week, number of whole and partial days missed during a 4-week period, and items that rate average coworker and self-work performance on a 10-point Likert scale (1=Worst performance to 10=Top performance). Hours spent in work over a 4-week period and over the last 7 days can be used to estimate absenteeism, and the HPQSF can also score presenteeism, a measure of actual performance in relation to possible performance. Self-reports on measure appear to match employer records of presence or absence (Kessler, Barber et al. 2003), and the HPQSF appears to be reliable between one time point and another (reliability of 0.52) and is sensitive to change (Kessler, Ames et al. 2004). The HPQSF takes approximately 5 minutes to complete.

8.6 Safety Assessments

Additional visits or repeat assessments (in person, at home, by telephone, or via tele-assessment) may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the potential participant.

8.6.1 Suicidal Ideation and Behavior Risk Monitoring

Suicidal ideation and behavior are disease related events with high incidence in populations of people with PTSD, especially those suffering from chronic PTSD. Participants will be monitored and observed closely for increases in suicidal ideation and behavior (SIB) or any other unusual changes in behavior. Participants are asked to report on their suicidality in therapy sessions and frequent phone calls. They may experience intense emotional responses to recalling and speaking about this material. Participants who experience increases in SIB should undergo a risk assessment.

Baseline assessment of suicidal ideation and behavior/intervention-emergent suicidal ideation and behavior will be monitored during the study using the MAPS Adapted C-SSRS.

8.6.1.1 MAPS Adapted Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [154]. It consists of a Baseline/Screening

version and a Since Last Visit version that assess suicidal ideation, ideation intensity, and behavior. The C-SSRS consists of a series of questions and can be administered during a face-to-face interview or over the telephone. The Baseline/Screening version will only be administered at the initial Screening visit. All subsequent administrations will utilize the Since Last Visit version. Participants who are discontinuing medications to participate in the study will complete the C-SSRS before and after medication washout. The C-SSRS Intensity scale obtained a Cronbach's alpha of 0.94 for the Since Last Visit form, and Last Visit C-SSRS severity scores were positively correlated with the BDI "suicide thoughts" item [155]. The MAPS Adapted C-SSRS was developed utilizing Dr. Kelly Posner's Columbia Suicide Severity Scale. The MAPS Adapted C-SSRS maintains the content and flow of the standard C-SSRS. The scale was adapted to modify formatting and add additional administrative guidance to reduce rater and data entry errors. The MAPS Adapted C-SSRS has been approved by Dr. Posner for use in MAPS Research and is referred to throughout the protocol as C-SSRS. The MAPS Adapted C-SSRS takes approximately 10 minutes to complete.

8.6.2 Physical Examinations

A physical examination will be symptom-directed and include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Traumatic Brain Injury (TBI) assessment with residual neurological signs or symptoms should be included as part of the neurological exam. Height and weight will also be measured and recorded, which will be used to calculate Body Mass Index (BMI). Investigators should pay special attention to clinical signs related to previous serious illnesses. A member of the therapy team should not perform the physical exam.

8.6.3 Vital Signs

Vital signs will be measured after 5 minutes rest in a semi-supine position and will include temperature, systolic and diastolic blood pressure, and pulse.

Additional at-home blood pressure measurements may be required to corroborate or rule out undiagnosed hypertension or to determine if an ongoing diagnosis of hypertension is controlled, and as required per the eligibility criteria of this protocol.

8.6.4 Electrocardiograms

12-lead ECG(s) will be obtained after 5 minutes of rest in a semi-supine position. ECGs will be collected in triplicate at the timepoints outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. A 1-minute rhythm strip will also be obtained to screen out participants with arrhythmias at baseline. ECGs are required for screening only but may be repeated during the study if clinically indicated.

8.6.4.1 Additional Cardiac Screening

If the potential participant has cardiac risk factors (e.g., well-controlled hypertension, diabetes mellitus) and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam or ECG, and if the investigator judges their overall health and other cardiovascular risk factors to be acceptable (family history, smoking, lipid levels, body weight, level of physical activity), they will be referred for stress test with either echocardiography or nuclear imaging, and for carotid ultrasound.

If these tests fail to reveal evidence of significant vascular disease or other cardiac disease, the person may be enrolled if there are no other contraindications. Additional cardiovascular testing to confirm eligibility may be performed in consultation with Medical Monitor. The investigators will record and review medications used to control hypertension prior to enrollment.

8.6.5 Clinical Laboratory Tests

Laboratory assessments, detailed in Table 9: Protocol-required Screening Laboratory Tests, with the exception of urine pregnancy and drug tests, will be performed at a clinical laboratory near the study site. Clinical laboratories for each site will be specified in a separate document. Certificates and normal ranges will be stored in the site's Investigator Site File (ISF).

The site physician will confirm laboratory assessments gathered in screening for assessing eligibility. The site physician will use the list of normal ranges to conclude whether participants are eligible for the protocol and will indicate justification for admitting participants with abnormal values after consultation with the Medical Monitor.

The protocol does not prescribe any post-dosing clinical laboratory assessments. Additional clinical laboratory tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

- If follow-up clinical labs are collected, record any clinically significant changes occurring during the study as an AE.
- All laboratory tests with values considered clinically significant during participation in the study should be repeated until the values are no longer considered clinically significant by the investigator or Medical Monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Table 9: Protocol-required Screening Laboratory Tests, must be conducted in accordance with the Laboratory Manual
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, should not exceed 20 mL.

Table 9: Protocol-required Screening Laboratory Tests

Laboratory Tests	Parameters

Hematology	• Hematocrit
	• Hemoglobin
	• Red Blood Cell (RBC) indices:
	  ○ RBC count
	  ○ Percentage and absolute differential counts
	  ○ Red cell distribution width (RDW)
	  ○ Mean corpuscular volume (MCV)
	  ○ Mean corpuscular hemoglobin (MCH)
	  ○ Mean corpuscular hemoglobin concentration (MCHC)
	• White blood cell (WBC) indices:
	  ○ RBC count
	  ○ Percentage and absolute differential counts
	  ○ Neutrophils
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils

Clinical chemistry	• Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Albumin, serum • Albumin:Globulin (A:G) ratio • Alkaline phosphatase • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Bilirubin, total and direct • Blood urea nitrogen (BUN): creatinine ratio • Calcium, serum • Carbon dioxide • Chloride, serum • Globulin, total • Glucose, fasting • Potassium, serum • Protein, total, serum • Sodium, serum
Routine urinalysis	• Specific gravity, color, appearance • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
Pregnancy testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (for PABP only)[1]
Other screening tests	• Thyroid Stimulating Hormone (TSH) with reflex free T3 and T4 • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines)
[1] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.	

Investigators must document their review of each screening laboratory report.

8.6.6 Pregnancy Testing

- Pregnancy testing is required for participants that are a person able to become pregnant (PABP) as defined in Appendix 2: Contraceptive and Barrier Guidance.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the time points as specified in the SoA.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.6.7 Remote Visits

Some of the non-drug therapy sessions and online evaluations may be permitted remotely, via tele-assessment (online video meetings), rather than at the study site. Remote visits if deemed appropriate may be permitted based on prior experience or in the context of local regulation due to a pandemic. There may be benefits to remote visits, such as convenience and reduced risk of COVID-19 transmission. There may be risks, including potential breach of security and technological difficulties or interruptions.

8.7 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an Adverse Event (AE) or Serious Adverse Event (SAE) and remain responsible for following up on all AEs.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

8.7.1 AE Definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

8.7.1.1 Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of any underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected dosing error of either study intervention or a concomitant medication. A dosing error will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

8.7.1.2 Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition or meet other prespecified reporting criteria.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure may fit the criteria for an AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Expressions of emotion or other emotional descriptions which are consistent with what would be expected during a therapeutic interaction with a participant meeting the eligibility criteria related to PTSD, unless participant reports effects interfere with daily activities.
    - Limited examples of this include euphoria, positive mood, compassion for self, compassion for others, intellectual efficiency, calmness, talkative, open to new experiences, meaningful experience.

8.7.2 SAE Definition

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

1. Results in death.
2. Is life threatening.
    - The term life threatening in the definition of SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the

event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent or significant disability/incapacity.
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect.
6. Other situations:
   - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

8.7.3 Adverse Events of Special Interest (AESI)

In accordance with the guidance Clinical Safety Data Management Definitions and Standards for Expedited Reporting ICH Topic E2A: Guidance for Industry or FDA Safety Reporting Requirements for INDs and BA/BE Studies, the sponsor will pay special attention to a subset of AEs. These AEs will be marked in the eCRF with the denotation "Adverse Event of Special Interest" (AESIs) whether serious or non-serious.

A subset of AEs will be collected in order to assess signals of cardiovascular risk for the IMP in the intended patient population that could be indicative of QT interval prolongation or cardiac arrhythmias, including Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, non-postural syncope, and seizures.

A subset of AEs involving suicide risk will be collected as AESIs whether serious or non-serious. These AESI terms include:

- Suicides
- Suicide attempts
- Self-injurious behavior associated with suicidal ideation
- Suicidal ideation judged to be serious or severe in the opinion of the investigator

In order to assess signals of abuse potential for the IMP in the intended patient population:

- AESIs involving the terms of Behavioral addiction, Drug abuser, Substance abuser, Dependence, Intentional product misuse, Overdose (accidental, intentional, or prescribed), or Drug diversion in cases that are related to MDMA or "Ecstasy" (unregulated material presented as MDMA) will be collected and coded as AESIs in the eCRF.
- Cases of noncompliance, protocol violations, participants lost to follow-up, and any other reasons why participants dropped out of the study will be assessed for presence of AESIs.
- Qualitative urine drug test data will be collected prior to each Experimental Session. Any positive findings that cannot be attributed to pre-approved concomitant medications or

diet will be reviewed by the Medical Monitor to assess compliance with ongoing eligibility criteria and for presence of AESIs.

If an AESI is a SAE or if it involves suicide risk, it should be reported within 24 hours of the site's awareness of the event.

8.7.4 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the study termination visit at the timepoints.

All AEs will be collected from initial study enrollment (in participants who meet eligibility criteria following screening) until the study termination visit at the timepoints specified in SoA.

Medical occurrences that begin before the start of Visit 0 but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.7.5 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.7.6 Recording and Follow-Up of AE and/or SAE

8.7.6.1 AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor, RA, or EC. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.7.6.2 Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild**: No limitation in normal daily activity.
- **Moderate**: Some limitation in normal daily activity.
- **Severe**: Unable to perform normal daily activity.

8.7.6.3 Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. The relationship of study treatment to an AE will be determined by the investigator based on the following definitions:

1. "Not Related": The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e., there are no facts, evidence, or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition.

2. "Related": The administration of the investigational product and AE are considered reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE or is the most likely cause of the AE. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- Following an initial report, the investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.7.6.4 Further Evaluation and Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up, as defined in Section 7.3 Lost to Follow-up.

8.7.7 Reporting of SAEs

8.7.7.1 SAE Reporting via Paper Data Collection Tool

- Email transmission of the electronic SAE Form (paper data collection tool) is the preferred method to transmit this information to the Medical Monitor or study CRA. A scanned copy of a printed SAE form may be accepted if the electronic form cannot be submitted.
- In rare circumstances and in the absence of email equipment, notification by telephone is acceptable with a copy of the SAE Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Form within the designated reporting timeframes.
- Contacts for SAE reporting can be found on the title page of this document (the Medical Monitor) or in the sponsor contact list provided separately.

8.7.8 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and notify the IRB/IEC, if appropriate according to local requirements.

8.7.9 Pregnancy

- Details of all pregnancies in participants will be collected after the start of study intervention and until the participant's final visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.7.8 Regulatory Reporting Requirements for SAEs. While the investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will not undergo any additional MDMA-assisted therapy sessions, though in some cases may continue participation in non-drug therapy sessions. Prior to continuation of non-drug study interventions following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.7.10 Disease-related Events

The following disease-related events (DREs) are common in participants with PTSD and can be serious/life threatening:

- Self-injurious behavior associated with suicidal ideation
- Suicidal ideation scores of 4 or 5 on the C-SSRS
- Suicidal ideation judged to be serious or severe in the opinion of the investigator

These events involve the exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition that would normally be appropriately recorded as AEs/AESIs. Because these events are associated with the disease under study, they would typically not be reported in an expedited manner to RA/ECs ahead of the annual reporting as part of the DSUR according to standard guidance for expedited reporting.

However, if any of the following conditions applies, then the event must be recorded as an AE/SAE (instead of a DRE) and reported in an expedited manner as appropriate:

1. The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.
2. The investigator considers that there is a reasonable possibility that the event was related to study intervention.
3. The applicable RA/EC has requested expedited reporting of these DREs.

Note: The FDA has requested that the current clinical development program submit expedited reports for these DREs related to suicidality. Therefore, these DREs reported in this protocol *will*

be reported to the FDA in an expedited manner as described in Section 8.7.3 Adverse Events of Special Interest.

8.7.11 Interruptions and Arrangements Due to COVID-19 Pandemic or Any Other Unforeseen Emergency at Clinic Locations

This clinical trial may be impacted by the Coronavirus Disease 2019 (COVID-19) global pandemic. Special arrangements may be required for study continuation and participant and study site staff safety due to this or any other unforeseen emergency in the future. The following accommodations in the protocol will be allowed, captured, and noted in the Clinical Study Report as COVID-19 deviations when applicable:

- Integrative Sessions may be conducted by tele-assessment.
- Delaying the start of medication tapering after enrollment and the subsequent Treatment Period per Section 6.8.1 Psychiatric Medications.
- Delaying Experimental Sessions and associated Integrative Sessions.
- Delaying IR assessments for participants who cannot complete them remotely off-site.
- Use of prohibited medications and/or cannabis or initiation of new therapy for participants with significant study delays, which will be reviewed by the study team before each Experimental Session and re-tapered prior to resuming treatment per Section 6.8 Concomitant Therapy.

For any participant with COVID-19 related illness, continued trial participation after full recovery of the disease may be appropriate after discussion between the site physicians and Medical Monitors on a case-by-case basis.

8.8 Other Assessments

8.8.1 Pharmacokinetics

PK parameters are not evaluated in this study.

8.8.2 Genetics

Genetics are not evaluated in this study.

8.8.3 Biomarkers

Biomarkers are not evaluated in this study.

8.8.4 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8.5 Medical Resource Utilization and Health Economics

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will:

- Include the reasons and duration of hospitalizations and emergency room visits.
- Exclude procedures, tests, and encounters mandated by the protocol.

The sponsor may use the collected data to conduct economic analyses.

9.0 Statistical Considerations

The Statistical Analysis Plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

No formal hypothesis testing will be conducted.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set (FAS)	• All enrolled participants.
mITT	• All participants who receive IMP in at least one Experimental Session and have at least one follow-up assessment.
Safety analysis set	• All participants who are exposed to study intervention.

9.3 Statistical Analyses

9.3.1 General Considerations

Data will be summarized to provide descriptive information on safety, tolerability, and effectiveness. Descriptive and summary statistics will be performed, as appropriate. Statistics will include number of observations, mean, standard deviation, median, range, and inter-quartile range for continuous variables, and the number and percent for categorical variables; 95% or 90% confidence intervals will be presented where appropriate. Additional statistics such as geometric mean and coefficient of variation (CV%) may be calculated as warranted. Demographics and baseline characteristics (e.g., age, sex, race, ethnicity, body weight) will be summarized using descriptive statistics.

The reasons for all discontinuations will be tabulated and grouped by treatment group and major reason. All deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment will be described.

9.3.2 Primary Endpoint Analysis

The primary endpoint is the change in mean CAPS-5 Total Severity Scores from Baseline to Primary Outcome Visit. Analysis of the primary endpoint will be conducted using a an ANCOVA model with change from baseline score as the outcome and baseline CAPS-5 score as an independent variable. Adjustment for additional potential covariates will be explored. Additional details will be provided in the SAP.

9.3.3 Secondary Endpoint Analysis

The key secondary endpoint is the change in mean SDS score from Baseline to Primary Outcome Visit.

Analysis of the secondary and exploratory outcomes will be conducted in the same manner as the primary efficacy analysis. Adjustment for potential covariates will be explored.

9.3.4 Exploratory Endpoints Analyses

An exploratory responder analysis will characterize clinical significance of PTSD treatment effect from Baseline to Primary Outcome Visit based on the following categories:

- **Treatment Response**: 10-point or greater reduction in CAPS-5 Total Severity Score.
- **Loss of Diagnosis**: 10-point or greater reduction in CAPS-5 Total Severity Score and no longer meeting PTSD diagnostic criteria on CAPS-5.
- **Remission**: CAPS-5 Total Severity Score of under threshold or less and no longer meeting PTSD diagnostic criteria on CAPS-5.

Exploratory sub-group analyses may be conducted when possible to evaluate effectiveness by treatment group and individual demographic characteristics (e.g., age, gender, ethnicity, index trauma, dissociative subtype of PTSD, presence of secondary traumatic stressors during the assessment period with LEC-5, diagnosis of comorbid depression, diagnosis of comorbid psychiatric diagnosis, group cohort, and number of Experimental Sessions completed). Exploratory analyses of secondary outcome measures will be described in the Statistical Analysis Plan.

9.3.5 Safety Analyses

AEs: AEs will be mapped to preferred term and system organ class using the most up to date Medical Dictionary for Regulatory Activities. AEs that begin after the first administration of study drug or existing AEs that worsen after the first dose of study medication are considered Treatment Emergent AEs (TEAEs). The number and percentage of participants reporting TEAEs will be summarized by system organ class and preferred term, by severity, and by relationship to study drug. The number and percentage of participants with SAEs, and the number and percentage of participants with AEs leading to treatment discontinuation will also be summarized by MedDRA system organ class and preferred term. Clinically significant changes in physical examination, laboratory parameters, vital signs, ECG, psychiatric health, withdrawal, and suicidality will be reported as AEs.

Concomitant medications: Concomitant medications will be coded using WHO Drug Dictionary and will be classified by Anatomical Therapeutic Chemical classification level 4 and preferred term for the Safety Analysis Set. Frequencies and percentages of participants using will be presented. All medication use will be listed regardless of the timing of the start of the medication.

Vital signs: Vital signs will be summarized using descriptive statistics of actual values and changes from baseline over time. The incidence of clinically notable vital signs will be summarized. Continuous laboratory data will be examined for trends using descriptive statistics of actual values and changes from baseline over time. These data will also be categorized as low, normal, or high based on the reference ranges of the central laboratory. Shift tables from baseline to each post baseline time point will be presented.

Suicidality: For each subject, C-SSRS data will be categorized into (1) suicidal ideation (nonspecific, method but no intent or plan, method and intent but no plan and method, intent and plan) and (2) suicidal behavior (suicide attempt, interrupted attempt, aborted attempt and preparatory acts and non-suicidal self-injurious behavior) at each visit. An increase in suicidality (i.e., passive suicidal ideation defined as an onset of suicidal ideation or behavior, or active suicidal behavior defined as an escalation from suicidal ideation to suicidal behavior) in a subject will be reported as an AE. The percentage of participants with passive suicidal ideation and active suicidal behavior will be presented by visit.

9.3.6 Other Analyses

Any additional analyses will be outlined in the SAP.

9.4 Interim Analysis

There is no interim analysis for this protocol.

9.5 Sample Size Determination

Approximately 60 participants will sign an ICF and be screened to achieve 18 (in three cohorts of up to 6) enrolled to study intervention.

Previously published trials with similar eligibility criteria have a post-ICF ineligibility rate of ~62% for individual MDMA-assisted therapy. With additional criteria to accommodate scheduling for a group study, the investigators anticipate up to a ~66% attrition following ICF. Therefore, the protocol will permit ICF and screening of up to 60 participants to achieve 18 participants enrolled to study intervention. The sample size is not based on achieving a certain degree of power for statistical test as this is a feasibility study.

Note: Enrolled means a participant, or their legally acceptable representative, has agreed to participate in the clinical study following completion of the informed consent process and eligibility screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered as enrolled if the informed consent is not withdrawn prior to participating any study activity after screening.

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Financial Disclosure

Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or their representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The study record must include documentation that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative (LAR).
- Participants who are rescreened are required to sign a new ICF.
- If applicable, the ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Ongoing Safety Data Review Committee

- Participant safety will be continuously monitored by the sponsor's internal Medical Science and Safety team.
- In addition, an aggregated safety data review that includes safety signal detection will be performed as part of the sponsor's standard operating procedure for the MDMA development program, per the sponsor's SOP.
- For trials with a Data Monitoring Committee, safety review will occur per the DMC charter and applicable sponsor SOP.

Dissemination of Clinical Study Data

Study data and results will be posted in accordance with applicable local regulations (e.g., 42 CFR, Part 11.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the Data Entry Manual.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Data Safety Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 7 years unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous or current medical records or transfer records, depending on the study.
- Definition of what constitutes source data and its origin can be found in the Data Safety Monitoring Plan.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or clinical trial agreement, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included in the study completed earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

The sponsor recognizes the importance of communicating medical research and scientific data and their obligations to participants enrolled in a study and therefore, encourage publication of such material in reputable scientific journals and at professional and/or academic seminars or conferences.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In that case it is intended that the first publication of the study's primary clinical data be co-authored by designated participating centers and the sponsor or designated representatives. Inclusion of Clinical Investigators in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the Study.
- All publications will follow International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, unless other guidelines are required by the journal. It is understood by the Clinical Investigators that the information generated in this study will be used by the sponsor in connection with the development of the IMP and therefore may be disclosed to government agencies in various countries.
- To allow for the use of information derived from the study, it is understood that the investigators are obliged to provide the sponsor with complete test results, all study data, and access to all study records.
- It is mandatory that all data analysis is done on the official monitored sponsor database and that the analysis plan is agreed upon with the sponsor statistician and follows the SAP where applicable.

- Any results of medical investigations with the sponsor and/or publication/lecture/manuscripts based thereon shall be exchanged and discussed by the investigator and sponsor prior to submission for publication or presentation.
- Due regard shall be given to the sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patient protection, coordinating, and maintaining submissions to health authorities, and coordinating with other ongoing studies in the same field.
- The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Trial Agreement.

Appendix 2: Contraceptive and Barrier Guidance

Participants in the following categories are considered a person able to become pregnant (PABP), i.e., fertile:

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in PABP not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - PABP on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance

Contraceptive use by either partner should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly effective methods of contraception are defined as those with a failure rate of <1% per year when used consistently and correctly.

Refraining from sexual activity periodically (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

Contraceptives Allowed During the Study Include:

Highly Effective Methods That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [A] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) [A] • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) [B]
Highly Effective Methods That Are User Dependent

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [A]
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation [A]
  ○ Oral
  ○ Injectable
• Refraining from engaging in sexual activities that lead to pregnancy [C]

[A] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. [B] Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. **Note**: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. [C] This is considered a highly effective method only if defined as occurring over the entire period of risk associated with the study intervention. Reliability needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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