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A Phase 2, Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Therapy in U.S. Veterans with Chronic PTSD

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USE	In conjunction with relevant Food and Drug Administration (FDA) guidance

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MPVA6 Protocol Synopsis

Full protocol begins on Page 10.

Rationale

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to therapy in patients with posttraumatic stress disorder (PTSD). PTSD is a serious debilitating disorder that negatively impacts a person's daily life, and can result in diminished cognitive and psychosocial functioning, fractured relationships, inability to maintain employment, substance abuse, high-cost healthcare utilization, increased depression, and suicide risk. People who suffer from PTSD relive their traumatic experience(s) through nightmares and flashbacks, have difficulty sleeping, and feel detached or estranged. Symptoms can be severe and long lasting.

MDMA is a monoamine releaser and re-uptake inhibitor with indirect effects on neurohormone release. The combined neurobiological effects reduce defenses and fear of emotional injury, enhance communication and introspection, and increase empathy and compassion. MDMA may enhance fear extinction learning in humans. The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process. Data from an international series of Phase 2 pilot studies of MDMA-assisted therapy conducted by the sponsor provide preliminary evidence that chronic PTSD, independent of cause, is treatable with two to three sessions of MDMA-assisted therapy and associated non-drug preparatory and integrative therapy. This open-label comparative effectiveness study will serve to explore the relative effectiveness of two vs. three randomly assigned active drug sessions in a sample of U.S. military veterans with chronic PTSD.

The rationale for the proposal to study two versus three active drug sessions builds in part on results of a previous randomized Phase 2 pilot study supported by MAPS [1]. This study found mixed results regarding the optimal number of MDMA-assisted sessions. Two active dose (100 mg and 125 mg) groups showed further clinically significant reductions in PTSD symptoms after a third Experimental Session, whereas a low dose (40 mg) group demonstrated significant reductions after open-label crossover to two active doses but did not continue to improve after a third. The authors concluded that more research is needed to determine the optimal number of treatment sessions in order to achieve symptom remission.

This trial will also help establish the effectiveness of MDMA-assisted therapy for PTSD in an ethnically diverse military veteran population in the context of a large Veteran's Affairs outpatient mental health clinic. A randomized, Phase 2 pilot trial provided preliminary evidence for the efficacy of MDMA-assisted therapy for chronic PTSD in military personnel and first responders [2]. The sample in that study (n=26) was primarily White (85%) and treated at a private outpatient clinic in the southern U.S. This study represents the first trial of MDMA-assisted therapy for PTSD in a treatment seeking veteran population in an outpatient VA mental health clinic. The James J Peters VA Medical Center is located in a large urban area (Bronx, NY) with a patient population that is approximately 55% Hispanic, and 60% Black or African American, 35% White, and 5% Asian. Results from this study will thus extend the findings of prior studies with the potential to inform treatment development and policy within the national VA system.

In addition to the primary aim of assessing the comparative effectiveness of two vs. three

Experimental Sessions, this study will include collection of blood samples for biomarker research from participants at two time points (pre- and post-treatment) in order to bank samples for future assay. The collection and banking of blood samples in association with treatment will allow for future exploratory analyses of potential biological markers that predict, mediate, or change in association with changes in PTSD symptom severity following MDMA-assisted therapy for PTSD.

In addition, the study will gather supportive data on the safety and effectiveness of manualized MDMA-assisted therapy while providing an opportunity for clinical supervision to therapy pairs to explore reproducibility of findings in a multi-site format to confirm the Phase 2 study design.

Study Design

This open-label, randomized study will assess the comparative effectiveness of two versus three active MDMA-assisted sessions in U.S. military veterans with at least moderate chronic PTSD treated in an outpatient VA treatment clinic. The study will be conducted in up to 60 participants, randomized with a 1:1 allocation to each treatment group.

There will be one or more two-person therapy pairs. During the lead-in portion of the study, each therapy pair will treat one participant who will be randomized in a 1:1 fashion to receive either 2 Experimental Sessions or 3 Experimental Sessions. The sponsor will provide clinical supervision for therapy pairs treating participants. Each new therapy pair participating in the trial will receive clinical supervision at three dedicated time points during treatment of their first subject and additional supervision as needed in subsequent cases. The sponsor's Adherence Raters and trainers will monitor videos of study visits for adherence to the therapeutic method and provide supervision.

A divided-dose of 160 mg MDMA HCl, with an initial 120 mg dose, followed by a supplemental dose of 40 mg approximately an hour and a half after the first dose, unless tolerability issues emerge, is administered during the Treatment Period with manualized therapy in two or three open-label monthly Experimental Sessions. Participants will be randomized to a 2-session group or a 3-session group. Each Experimental Session is followed by three Integrative Sessions of non-drug therapy. Experimental Sessions are followed by an overnight stay.

The Primary Outcome measure, the change in CAPS-5 from baseline, is assessed by a centralized, blinded Independent Rater (IR) pool at post-treatment for each group. The IR pool will be blinded to visit number and number of treatments received and will not have access to data collected during the active treatment period. The CAPS-5 will be repeated one month following the final treatment session (post-treatment). Blood samples will be collected at three timepoints: a clinical laboratory blood draw at Screening, and biomarker research blood draw pre- and post-treatment. Self-reported PTSD and depression symptoms will be assessed at numerous visits by the PCL-5 and BDI-II (see Tables 7 and 8). The blood samples collected at baseline and post-treatment will be banked for future analysis for a sub-study described in a separate protocol. For each participant, the study will consist of:

- **Screening Period (~4 weeks)**: Phone or in person screen, informed consent, eligibility, and baseline assessment
- **Preparatory Period with Enrollment Confirmation (at least 7 days, max time dependent upon medication tapering)**: medication tapering, Preparatory Sessions and Baseline assessments leading to Enrollment Confirmation.
- **Study Enrollment and Randomization:** Include eligible participants, randomize to group, complete baseline self-report measures, collection of pre-treatment biomarker

blood samples

- **Treatment Period (Group 1: 9-15 weeks, Group 2: 6-10 weeks):** Each Experimental Session followed by 3 non-drug Integrative Sessions.
- **Post-treatment (~4 weeks)**: At one-month post final Integrative Session, clinical evaluation and self- report measures, collection of post-treatment biomarker blood samples.
    - For the 2-session group: additional clinical evaluation one month following post-treatment as a secondary outcome.
- **Study Termination:** After the Study Termination visit, participants will have the opportunity to enroll in a separate LTFU study at least six months from the final Experimental Session.

Participants will be recruited through the James J Peters VA Medical Center PTSD Clinic, which is housed in an outpatient mental health clinic, from providers who treat veterans, or from organizations that serve veterans. The sponsor will monitor demographics on an ongoing basis and encourage diversity (representative of PTSD population) in enrollment of study participants by communicating with the site. Recruitment efforts may also potentially include print and internet advertisements, flyers posted in the mental health clinic, and recruitment of former research participants in PTSD studies.

Qualified, blinded IRs selected based on availability from the IR Pool will perform the CAPS-5 assessments as described in the following table.

CAPS-5 Data Collection by Visit

CAPS Number	Visit	Description/Timing	Target Timing Post Baseline
Baseline CAPS-5T1	V3	Baseline between Visits 2 and 4 (Preparatory Sessions), after medications have been tapered.	Not Applicable
CAPS-5 T2	V13 (2-session group) or V17 (3-session group)	Post Treatment Primary Outcome 49 to 56 days after last Experimental Session	63 to 98 days or 85 to 134 days
CAPS-5 T2.2	V15 *(2-session group only)*	Secondary outcome for 2-session group only 28 to 35 days after T2	85 to 134 days

Dose Selection

This study will compare the effects of two versus three open-label manualized Experimental Sessions of therapy assisted by divided doses of MDMA HCl (referred to as MDMA throughout) as described in the table below, along with associated non-drug preparatory and integrative therapy. Similar MDMA doses to those proposed in this study have been safely used in previous Phase 2 and 3 studies sponsored by MAPS.

Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	120 mg	40 mg	120 mg to 160 mg
2	120 mg	40 mg	120 mg to 160 mg
3	120 mg	40 mg	120 mg to 160 mg
Total Cumulative Dose: 2 Session Group			240 mg to 320 mg
Total Cumulative Dose: 3 Session Group			360 mg to 480 mg

* Unless tolerability issues emerge with the first dose or it is refused by the participant. Supplemental dose will be 40 mg for all subjects throughout the study.

Protocol Objective

The overall objective of this study is to use standard clinical measures to explore the relative effectiveness in reducing PTSD symptom severity comparing groups randomly assigned to two versus three Experimental Sessions of open-label MDMA-assisted therapy, in a diverse sample of U.S. military veterans with PTSD in a VA outpatient clinic, and to serve as an opportunity for supervision of therapy pairs selected to conduct MDMA-assisted therapy research.

Primary Objective

The primary objective of this study is to compare the effectiveness of two versus three sessions of MDMA-assisted therapy in treatment of PTSD, based on mean change in CAPS-5 Total Severity Score from T1 (Baseline) to T2 (Primary Outcome).

Secondary Objective

The key secondary objective of this study is to compare the effectiveness of two versus three sessions of MDMA-assisted therapy on -rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) items score from Baseline to T2 (Primary Outcome).

Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, and vital signs to support the package insert for MDMA-assisted therapy. The following safety objectives will evaluate the safety of MDMA-assisted therapy:

1. Assess incidence of AEs during Experimental Sessions 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.
2. Assess incidence of AEs by severity.
3. Assess incidence of Treatment Emergent AEs (TEAEs) from first dose through Study Termination by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and through 2 days after MDMA administration.
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.
6. Assess incidence of AEs by severity categorized as leading to discontinuation of MDMA, resulting in death or hospitalization, and continuing at Study Termination.
7. Assess incidence of SAEs.
8. Assess incidence of concomitant medications of interest taken during an Experimental Session and through 2 days after MDMA administration.
9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.
10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the C-SSRS.
11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-MDMA administration to end of each Experimental Session.

Recruitment and Participant Population

Previously published trials with similar eligibility criteria have a post-ICF ineligibility rate of ~62% for individual MDMA-Assisted Therapy. Therefore, therapists or consent delegates trained by the sponsor will enroll up to 175 open-label participants in this study. “Enrolled” is defined as having signed informed consent. Therefore, the protocol will permit ICF and screening of up to 175 participants to achieve 60 participants enrolled to study intervention. Up to 60 participants will be treated in the study. Participants will be recruited through the James J Peters VA Medical Center PTSD Clinic, which is housed in an outpatient mental health clinic, from providers who treat veterans, or from organizations that serve veterans. Recruitment efforts may also potentially include print and internet advertisements, flyers posted in the mental health clinic, and recruitment of former research participants in PTSD studies.

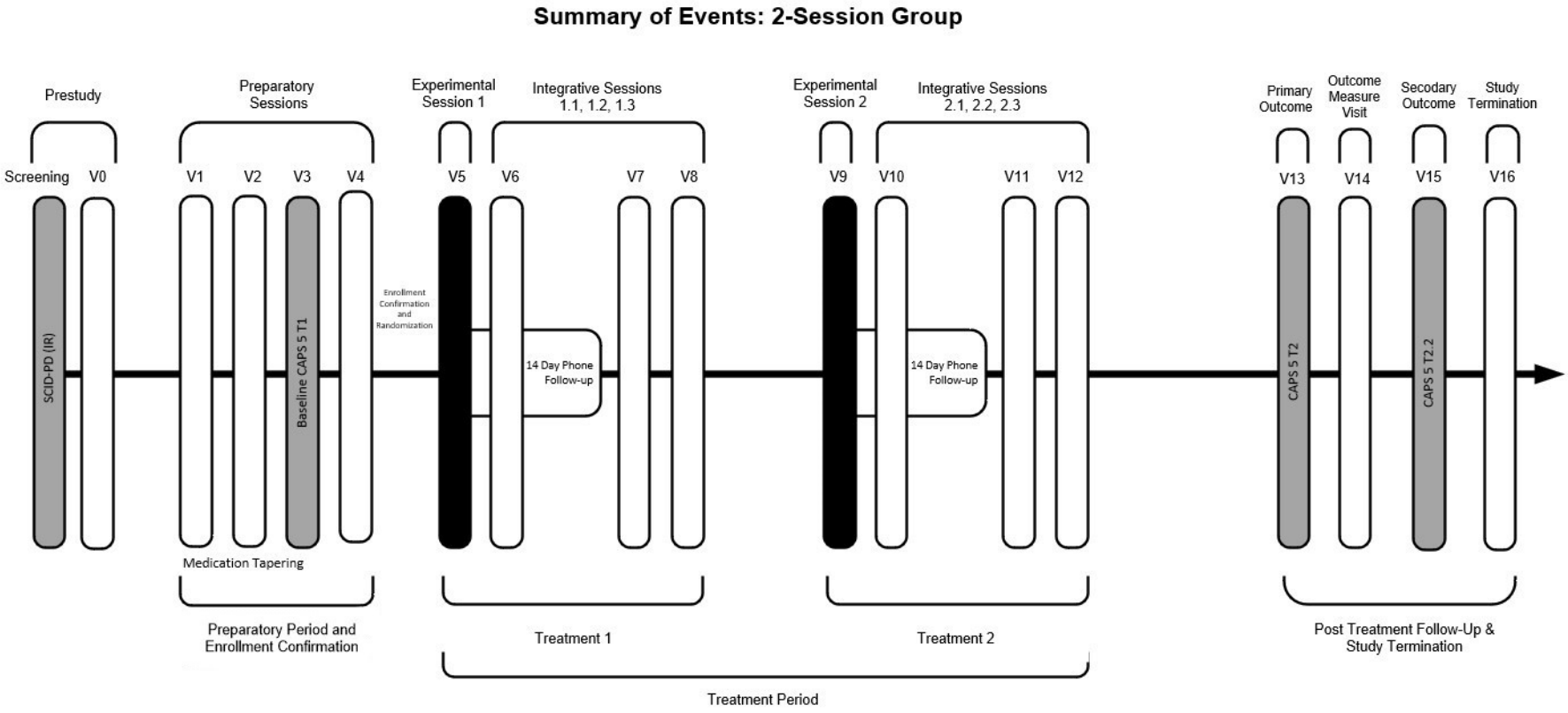
Participants will be U.S. military veterans aged 18 or older, with a confirmed diagnosis of PTSD with at least a 28 on the CAPS-5 with symptoms present for at least 3 months. Participants would not be excluded for having more than one traumatic event or for having tried, not tolerated, or refused a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) prescribed for PTSD. Participants with confirmed diagnosis of specific psychological and personality disorders will be excluded. Participants must be in good physical health and without major medical disorders that could affect the safety or tolerability of MDMA.

Statistical Analysis

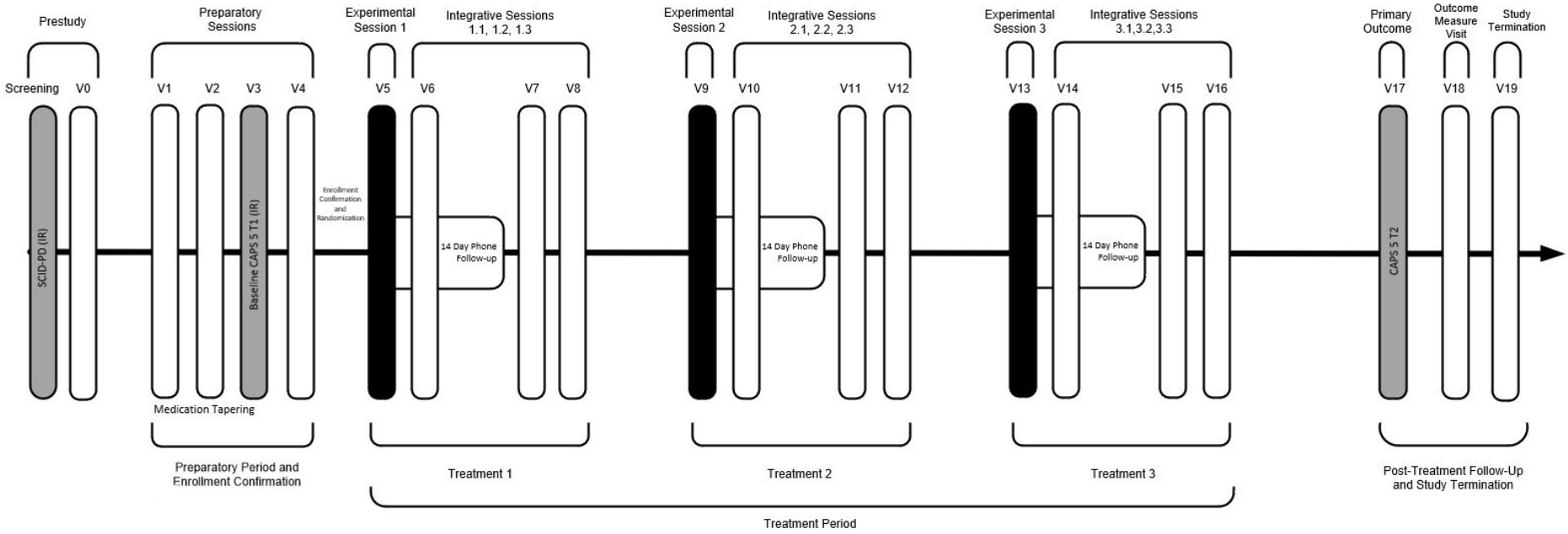
In this equivalence design the primary hypothesis is a comparison of 3 sessions of MDMA with therapy versus 2 sessions of MDMA with therapy. The internal validity of this study is predicated upon data already established and approved by the FDA showing that 3 sessions of MDMA with therapy has proven superiority over placebo in the treatment of PTSD. Therefore, it is appropriate to compare the effectiveness of the experimental arm of 2 sessions of MDMA to the effectiveness of the previously established 3 doses in order to test an equivalence hypothesis. If the null hypothesis is rejected, the alternative hypothesis will be accepted which states that 2 sessions of MDMA shows equivalent efficacy as 3 sessions. The measure of effectiveness is the change from baseline in the CAPS-5 Total Severity Score. In this equivalency design the "zone" of equivalence is a pre-defined region above or below the difference in mean changes in the CAPS-5 Total Severity Score in the arm given 3 sessions of MDMA. In a previous study, MP16, it was reported that the mean change in baseline among 29 participants with PTSD who were given 3 sessions of MDMA experienced a mean reduction of 30.7 in the CAPS-5 Total Severity Score, with a standard deviation of 12.7. Therefore, the "zone" of equivalence in this study is defined as a mean change in the CAPS-5 Total Severity Score in the arm given 2 sessions of MDMA that is within 11 points of the mean change in that seen in the arm given 3 sessions. If similar results are observed as those seen from the sponsor’s 3 session MP16 study, we would conclude equivalence if the difference in mean changes in CAPS-5 Total Severity Score in the arm given 2 sessions of MDMA was as low as -19.7 to as high as -41.7. Assuming that in the population of PTSD patients there is no difference in the mean change in CAPS-5 Total Severity Score when given 2 sessions of MDMA or 3 sessions of MDMA, with alpha level set at 5%, power set to 90%, the sample size of this study is 30 participants per arm.

The two treatment groups will be compared in post-treatment change in symptom severity, as assessed by the mean change in CAPS-5 Total Severity Score from T1 to T2. Exploratory responder analyses will also be conducted to determine whether each group obtained a clinically significant reduction in symptoms. The two treatment groups will be compared on change from baseline in functional impairment, as assessed by the mean change in SDS Score from T1 to T2. Details and additional exploratory analyses are described in the Statistical Analysis Plan.

Study Structure Overview



Summary of Events 3-Session Group



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List of Abbreviations

°C	Degrees Celsius
A:G	Albumin:Globulin
AAQ-II	Acceptance and Action Questionnaire–II
ACE	Adverse Childhood Experiences Questionnaire
ADHD	Attention Deficit/Hyperactivity Disorder
AE	Adverse Event
AED	Automatic External Defibrillator
AESI	Adverse Event of Special Interest
AHA	American Heart Association
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BDI-II	Beck Depression Inventory-II
BLS	Basic Life Support
BMI	Body Mass Index
BP	Blood Pressure
BPAQ-SF	Buss-Perry Aggression Questionnaire (Short-Form)
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
%CDT	%Carbohydrate-deficient Transferrin
CMC	Chemistry Manufacturing and Control
COVID-19	Coronavirus Disease 2019
CPGS	Chronic Pain Grade Scale
CRA	Clinical Research Associate
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
DMF	Drug Master File
DRRI-II	Deployment Risk & Resilience Inventory-2
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSP-I	Dissociative Subtype of PTSD Interview
DUDIT	Drug Abuse Disorders Identification Test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
ED	Emergency Department
EDC	Electronic Data Capture
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
ePRO	Electronic Participant Reported Outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

HIPAA	Health Insurance Portability and Accountability
HPA	Hypothalamic-pituitary-adrenal
HPMC	Hypromellose
IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IPF	Inventory of Psychosocial Functioning
IR	Independent Rater
IRDB	Independent Rater Database
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
kg	Kilogram
LEC-5	Life Events Checklist
LTFU	Long-term Follow-up
MAPS	Multidisciplinary Association for Psychedelic Studies
MAOI	Monoamine Oxidase Inhibitor
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MIES	Moral Injury Event Scale
MINI	Mini-International Neuropsychiatric Interview
mg	Milligram
*m*ITT	Modified Intent-to-Treat
mmHg	Milligrams of Mercury
MAPS PBC	MAPS Public Benefit Corporation
MMRM	Mixed Model Repeated Measure
ms	Millisecond
NOAEL	No-Observed-Adverse-Effect Level
OSU-TBI	Ohio State University Traumatic Brain Injury
PCL-5	PTSD Checklist for DSM-5
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
RACT	Risk Assessment and Categorization Tool
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
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
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SPGT	Serum Glutamic Pyruvic Transaminase
SRNU	Self-reported Nicotine Use

SSR	Sample size re-estimation
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid-stimulating Hormone
UFEC	Utilization of Facility-based and Emergent Care
U.S.	United States
VA	U.S. Department of Veterans Affairs
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization
WHO DDE	WHO Drug Dictionary Enhanced™
WHOQOL	World Health Organization Quality of Life Instruments

1.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor 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). Controlled Phase 1 studies, nonclinical studies, and investigator-initiated studies formed the basis for the Clinical Development Program of MDMA under Investigational New Drug (IND) #063384. MAPS-sponsored studies are implemented through MAPS' wholly owned subsidiary and delegate, the MAPS Public Benefit Corporation (MAPS PBC).

1.1 Rationale

PTSD is a serious debilitating disorder that negatively impacts a person's daily life. 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. This is supported by data from an international series of Phase 2 pilot studies of MDMA-assisted therapy conducted by the sponsor that provide preliminary evidence that chronic PTSD, independent of cause, is treatable with two to three sessions of MDMA-assisted therapy and associated non-drug preparatory and integrative therapy. This open-label comparative effectiveness study will serve to explore the relative effectiveness of two vs. three randomly assigned active drug sessions in a sample of U.S. military veterans with chronic PTSD. 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 results from multiple independent studies in Phase 2 efficacy analyses demonstrate superiority of MDMA-assisted therapy over therapy with placebo and low dose MDMA. The acceptable risk-benefit ratio in early trials justifies further study. The rationale for the proposal to study two versus three active drug sessions builds in part on results of a previous randomized Phase 2 pilot study supported by MAPS [1]. This study found mixed results regarding the optimal number of MDMA-assisted sessions. Two active dose (100 mg and 125 mg) groups showed further clinically significant reductions in PTSD symptoms after a third Experimental Session, whereas a low dose (40 mg) group demonstrated significant reductions after open-label crossover to two active doses but did not continue to improve after a third. The authors concluded that more research is needed to determine the optimal number of treatment sessions in order to achieve symptom remission.

This trial will also help establish the effectiveness of MDMA-assisted therapy for PTSD in an ethnically diverse military veteran population in the context of a large Veteran's Affairs outpatient mental health clinic. A randomized, Phase 2 pilot trial provided preliminary evidence for the efficacy of MDMA-assisted therapy for chronic PTSD in military personnel and first responders [2]. The sample in that study (n=26) was primarily White (85%) and treated at a private outpatient clinic in the southern U.S. This study represents the first trial of MDMA-assisted therapy for PTSD in a treatment seeking veteran population within an outpatient VA mental health clinic. The James J Peters VA Medical Center is located in a large urban area (Bronx, NY) with a patient population that is approximately 55% Hispanic, and 60% Black or African American, 35% White, and 5% Asian. Results from this study will thus extend the findings of prior studies with the potential to inform treatment development and policy within the national VA system.

In addition to the primary aim of assessing the comparative effectiveness of two vs. three Experimental Sessions, this study will include collection of biomarker blood samples from participants at two time points (pre- and post-treatment) in order to bank samples for future assays. Each blood draw will collect up to 160 mL. Samples will be frozen and stored in locked freezers within secure research laboratories at the following address:

James J Peters VA Medical Center
Research Building, 4th Floor
130 West Kingsbridge Road
Bronx, NY 10468

The collection and banking of blood samples in association with treatment will allow for future exploratory analyses of potential biological markers that predict, mediate, or change in association with changes in PTSD symptom severity following MDMA-assisted therapy for PTSD.

In this study, therapy pairs without previous experience on an MDMA-assisted therapy study will have the opportunity for clinical supervision. There will be one or more two-person therapy pairs. During the lead-in portion of the study Section 4.1 Proof-of-Principle Therapist Training Lead-In), each therapy pair will treat one participant who will be randomized in a 1:1 fashion to receive either 2 Experimental Session or 3 Experimental Sessions. This part of the study is designed to support and expand the knowledge and skills of therapy team members who will be working on MDMA research studies.

1.2 Background

1.2.1 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 [3]. 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 [4]. 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 undermodulation mediated by failure of prefrontal inhibition of the same limbic regions [5, 6]. 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.

Approximately 7% of the population in the United States (U.S.) will have PTSD sometime in their life, but this figure jumps to 10.8% to 13% of veterans with combat experience [7]. For soldiers returning from Iraq and Afghanistan, the incidence of PTSD is 17.1% with 400,000 to 500,000 U.S. Iraq/Afghanistan veterans reportedly having PTSD. In 2004, the Defense Department and U.S. Department of Veterans Affairs (VA) spent $4.3 billion on PTSD disability payments to approximately 215,000 veterans [8]. In 2012 alone the VA spent $294 million and $3 billion, respectively, on care for veterans with the disorder and disability payments, even with this funding the demand for services far outreached the availability of VA doctors and services. As of June 30, 2016, more than 868,000 veterans with a diagnosis of PTSD were receiving disability compensation for service-connected mental disorders, with an estimated cost of about $17 billion per year [9]. The most recent VA data from September 2018 reports that more than 1,039,000 vets receive disability payments for PTSD [10]. There are an estimated 20 to 22 suicides a day by veterans [11].

Available PTSD treatments, including medications and therapy, effectively treat only some of people who try them for adequate dose and duration. This indicates a need to develop treatments targeting durable remission of PTSD. The Food and Drug Administration (FDA) has approved only two pharmacotherapies for PTSD, 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 [12-14]. PTSD rarely remits after 12 weeks of SSRIs, and many patients who are placed on maintenance treatment experience partial relief of symptoms, which can 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). An extensive list of medications, namely antipsychotics, anxiolytics, antidepressants, and sleep aids, are frequently prescribed off-label but have only small effect sizes in reducing PTSD symptoms. PTSD brings a high public burden, both economically and socially, by increased use of health and social services, lost wages, and disability payments [15, 16]. Given the chronicity of PTSD, low compliance evidenced by high dropouts, and limited recovery with current medications contributing to serious outcomes, PTSD patients suffer from unmet medical need.

One treatment approach is to develop medications and/or therapeutic treatments that may address chronic hyperarousal and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis associated with PTSD. Trauma-based therapies, particularly prolonged exposure, and cognitive processing therapy are considered among the most effective therapies. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in treating symptoms of PTSD [17, 18], although some patients may need more than one type of treatment to reduce or resolve those symptoms. A meta-analysis concluded that all "bona fide" therapies, including those listed above, are similarly effective with PTSD [19]. In the past decade, there has been a growing amount of research into medications and other methods that may augment the effectiveness of therapy for PTSD (see [20] for a review). Examples of this are virtual reality-assisted exposure therapy [21, 22], and D-cycloserine-assisted psychotherapy [23]. MDMA-assisted therapy is another such approach.

1.2.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 [24, 25]. Similar to SSRIs, MDMA binds to the serotonin transporter, but has additional effects on carrier-mediated release and reuptake inhibition of serotonin and to a lesser extent in humans, norepinephrine and dopamine [26-32]. MDMA also increases levels of affiliative neurohormones oxytocin and vasopressin, which is hypothesized to increase trust and attenuate reactivity to threatening cues. Some researchers have suggested a role for oxytocin in treating PTSD. The indirect effects of MDMA on central and peripheral neurohormone levels contribute to a novel mechanism that may help regulate the HPA axis during therapy.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to two 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 doses of MDMA have 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 go well beyond anxiolytics and SSRIs. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (material represented as containing MDMA) [33, 34]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [35]. Hence, MDMA may have moderate abuse potential. See the Investigator's Brochure (IB) for a more detailed explanation.

1.2.3 MDMA-Assisted Therapy for PTSD

Many therapies for PTSD involve the extinction of abnormal autonomic responses through revisiting traumatic experiences in therapy with an appropriate level of emotional engagement [18]. To be effective, exposure must be accompanied by a degree of emotional engagement or "fear activation" while avoiding dissociation or overwhelming emotion [36]. This has been referred to as working within the "optimal arousal zone" or "window of tolerance" [37-39].

The combined neurobiological effects of MDMA increase compassion, 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, which is associated with heightened encoding of fearful memories, and decreases blood flow in the prefrontal cortex. In contrast, MDMA acutely decreases activity in the amygdala [40], and there is some indication that MDMA may increase activity in the prefrontal cortex [41]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [40]. This action is compatible with its reported reduction in fear or defensiveness and is in contrast to the activation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [42-44]. The reduction in stress-induced activation of the amygdala may be supported and enhanced by interacting with the therapy pair during and after the MDMA experience. The subjective effects of MDMA create a productive psychological state that enhances 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 [45-48]. 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 [49]. Participants are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. 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 the 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 Psychotherapy, which the new therapy pairs will be trained on prior to the study.

1.2.4 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 [50], with 80 to 160 milligrams (mg) MDMA required to produce desired subjective effects in humans [50, 51]. MDMA was found to robustly influence human emotional status in a unique way [50], without adversely affecting physiological functions or perception, such as visual perception or cognition [52-55]. In the 1970s, psychotherapists used MDMA-assisted therapy to treat psychological disorders, including anxiety [56]. Legal therapeutic use continued until its placement on the U.S. list of Schedule I substances in 1985 [46, 49, 57]. An estimated 500,000 doses of MDMA were administered during therapy and personal growth sessions in North America prior to its scheduling [46, 58]. A few uncontrolled human studies of MDMA assessing safety in a therapeutic setting occurred in the 1980s [59, 60].

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 [61, 62]. 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 [48]. These studies formed the basis of clinical experience with MDMA prior to studies subsequently conducted under a MAPS IND.

Under IND #063384, 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-IV score: 50+), with at least 6 months of symptoms. Participants were not excluded for having more than one traumatic event, or for having tried, not tolerated, or refused an SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) prescribed for PTSD. Outcomes from six Phase 2 studies with evaluable data have been promising and have generated a range of methodological information for the design of future studies.

Results from four Phase 2 studies have been published: one study in the U.S. with a long-term follow-up (LTFU) conducted an average of 3.8 years after the final MDMA-assisted therapy session (MP-1) [47, 63], one in Switzerland (MP-2) [64, 65], one in Charleston, South Carolina that enrolled veterans and first responders (MP-8) [2], and one in Boulder, Co (MP-12) [1]. MP-1 was followed by a small open-label extension study examining the treatment of relapse in three participants with a single MDMA-assisted therapy treatment and a 12-month follow-up (MP1-E2). An additional study conducted in Israel was completed (MP-9) and two international studies were terminated early for logistical reasons with partial datasets (MP-3, MP-4). These studies tested a range of designs, such as a placebo control (MP-1, MP-4), low dose MDMA comparator control (MP-2, MP-9), and three-arm dose response studies (MP-8, MP-12). MP-4 was terminated early due to delays in regulatory approval and enrollment timelines, with available efficacy data presented without a formal analysis. MP-3 was terminated early by the sponsor due to inadequate data collection procedures at the site and insufficient therapy team training; efficacy data are not available for these reasons (MP-3 is excluded from Phase 2 data).

Intent-to-treat (ITT) analysis of primary efficacy and safety data from six MAPS-sponsored MDMA PTSD Phase 2 clinical trials worldwide (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12) consisting of 107 blinded participants with chronic PTSD were completed in 2016[66]. 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 [67] 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-IV assessment [68].

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 [69]. In a 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. In comparison to an inactive placebo, divided-doses of 80+40 mg or 120+60 mg MDMA were statistically superior for PTSD treatment in CAPS-5 severity scores from Baseline to 2 months after three blinded experimental sessions ($p<0.0001$). 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 to encompass a larger sample of participants with moderate to severe PTSD.

As of October 01, 2021, with 358 individuals exposed to MDMA in the sponsor's development program across various indications and at least 1,441 participants in MDMA research studies conducted without sponsor support (for a total of at least 1,799 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.

2.0 Protocol Objectives

The overall objective of this study is to use standard clinical measures to explore the relative effectiveness in reducing PTSD symptom severity comparing groups randomly assigned to two

versus three Experimental Sessions of open-label MDMA-assisted therapy, in a diverse sample of U.S. military veterans with PTSD in a VA outpatient clinic, and to serve as an opportunity for supervision of therapy pairs selected to conduct MDMA-assisted therapy research.

2.1 Primary Objective

The primary objective of this study is to compare the effectiveness of two versus three sessions of MDMA-assisted therapy in treatment of PTSD, based on mean change in CAPS-5 Total Severity Score from T1 (Baseline) to T2 (Primary Outcome).

2.2 Key Secondary Objective

The key secondary objective of this study is to compare the effectiveness of two versus three sessions of MDMA-assisted therapy in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item score from Baseline to T2 (Primary Outcome).

2.3 Exploratory Objectives

Exploratory objectives include analyses of baseline predictors of treatment outcome (e.g., adverse childhood experiences, history of mild TBI), and post-treatment changes in self report measures of clinical state, including depression, PTSD, and moral injury as assessed by:

1. Explore changes between the two treatment groups in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal, as measured by changes in CAPS-5 subscale scores from Baseline to Post-treatment and Follow-up.
2. Explore trajectories of change and onset of treatment effectiveness within and between groups using multiple assessments with PCL 5 self-reports.
3. Explore the effect of adverse childhood experiences (ACE) on the CAPS-5 Total Severity analyses.
4. Explore differences between treatment groups using measures below regarding changes in clinical state associated with MDMA treatment, and regarding baseline predictors of outcome using the following measures:
    a. Acceptance and Action Questionnaire (AAQ-II)
    b. Dissociative Subtype of PTSD Interview (DSP-I)
    c. Columbia Suicide Severity Rating Scale (C-SSRS)
    d. Self Compassion Scale (SCS)
    e. Buss-Perry Aggression Questionnaire-Short Form (BPAQ-SF)
    f. Deployment Risk and Resilience Inventory 2 (DRRI-2)
    g. Life Events Checklist (LEC-5)
    h. PTSD Checklist for DSM-5 (PCL-5)
    i. Moral Injury (MIES)
    j. Depression (BDI-II)
    k. Posttraumatic Growth Inventory (PTGI)
    l. Chronic Pain Grade Scale (CPGS)
    m. World Health Organization Quality of Life-Brief Form (WHOQOL-BREF)
    n. Ohio State University Traumatic Brain Injury (OSU-TBI)
    o. The Utilization of Facility and Emergent Care (UFEC)
    p. Addictive behaviors including: Alcohol Use Disorders Identification Test (AUDIT), Drug Use Disorders Identification Test (DUDIT)

2.4 Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, and vital signs to support the package insert for MDMA-assisted therapy. The following safety objectives will evaluate the safety of MDMA-assisted therapy:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Product (IP), 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.
2. Assess incidence of AEs by severity.
3. Assess incidence of Treatment Emergent AEs (TEAEs) by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and through 2 days after IP administration.
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.
6. Assess incidence of AEs by severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination.
7. Assess incidence of SAEs.
8. Assess incidence of concomitant medications of interest taken during an Experimental Session and through 2 days after IP administration.
9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.
10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IP administration to end of each Experimental Session.

3.0 Eligibility Criteria

3.1 Inclusion Criteria

At the completion of Screening, participants must meet all eligibility criteria and agree to all lifestyle modifications to be enrolled. Each participant will then enter the Preparatory Period which includes medication tapering, if needed, and non-drug Preparatory Sessions. The Preparatory Period ends with Enrollment Confirmation. A participant's enrollment will be confirmed if they have completed medication tapering, have a confirmed PTSD diagnosis per the CAPS-5 assessment and a Total Severity Score of 28 or greater, a total PCL-5 score of 36 or greater at Screening, continue to agree to all lifestyle modifications, and continue to meet all eligibility criteria (those criteria marked with an * below will only be assessed at Screening, since they will not change).

Potential participants are eligible to enroll in the protocol if they:

1. *Are a U.S. military veteran at least 18 years old
2. *Are able to provide written, informed consent
3. *Are able to swallow pills
4. Agree to have study visits recorded, including Experimental Sessions, Independent Rater assessments, and non-drug therapy sessions

5. Must 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 a participant becoming suicidal or unreachable
6. Must agree to inform the investigators within 48 hours of any medical conditions and procedures
7. If able to become pregnant, must have a negative pregnancy test at study entry and prior to each Experimental Session, and must agree to use adequate contraceptive methods through 10 days after the last Experimental Session. Adequate contraceptive methods include intrauterine device (IUD), injected, implanted, intravaginal, or transdermal hormonal methods, abstinence, oral hormones plus a barrier contraception, vasectomized sole partner, or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e., condom plus diaphragm, condom or diaphragm plus spermicide, oral hormonal contraceptives plus spermicide or condom). 'Not able to become pregnant' is defined as permanent sterilization, postmenopausal, or assigned male at birth
8. Agree to the following lifestyle modifications (described in more detail in Section 3.3 Lifestyle Modifications): comply with requirements for fasting and refraining from certain medications prior to Experimental Sessions, not participate in any other interventional clinical trials during the duration of this study without prior approval of the Medical Monitor, remain overnight at the study site after each Experimental Session and refrain from driving until cleared by Therapist after Integrative Session the following day or be driven home by a support person or by taxi/car service, and commit to medication dosing, therapy, and study procedures

Medical History

9. *At Baseline, meet DSM-5 criteria for current PTSD with a symptom duration of 3 months or longer and have PTSD symptoms in the last month with a minimum CAPS-5 Total Severity Score of 28 or greater and a total PCL-5 score of 36 or greater at Screening
10. *At Screening, may have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if they pass additional screening to rule out underlying cardiovascular disease
11. *At Screening, may have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed
12. * May have current mild alcohol or cannabis use disorder (meets 2 or 3 of 11 diagnostic criteria per DSM-5) or moderate alcohol or cannabis use disorder in early remission for the 3 months prior to enrollment (meets 4 or 5 of 11 diagnostic criteria per DSM-5).
13. May have a history of or current Diabetes Mellitus (Type 2) if additional screening measures rule out underlying cardiovascular disease, if the condition is judged to be stable on effective management, and with approval by the Medical Monitor
14. May have hypothyroidism if taking adequate and stable thyroid replacement medication
15. May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist

3.2 Exclusion Criteria

Potential participants are ineligible to enroll in the protocol if they:

1. Are not able to give adequate informed consent
2. Are currently engaged in compensation litigation whereby financial gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorders

3. Are likely, in the investigator's opinion and via observation during the Preparatory Period, to be re-exposed to their index trauma or other significant trauma, lack social support, or lack a stable living situation
4. Have used Ecstasy (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the first Experimental Session; or have previously participated in a MAPS-sponsored MDMA clinical trial
5. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation
6. Have hypersensitivity to any ingredient of the IMP (Investigational Medicinal Product)

Psychiatric History

7. Have received Electroconvulsive Therapy (ECT) within 12 weeks of enrollment
8. Have a history of or a current primary psychotic disorder, bipolar disorder 1 assessed via MINI and confirmed via clinical interview or dissociative identity disorder assessed via DDIS and confirmed via clinical interview
9. Have a current eating disorder with active purging assessed via MINI and clinical interview
10. Have current major depressive disorder with psychotic features assessed via MINI
11. Have a current moderate (not in early remission in the 3 months prior to enrollment; meets 4 or 5 of 11 diagnostic criteria per DSM-5) or severe alcohol or cannabis use disorder within the 12 months prior to enrollment (meets at least 6 of 11 diagnostic criteria per DSM-5)
12. Have an active illicit drug or prescription drug substance use disorder at any severity (other than cannabis) within 12 months prior to enrollment
13. Have current Personality Disorders Cluster A (paranoid, schizoid, schizotypal), Cluster B (antisocial, borderline, histrionic, narcissistic), or Cluster C (avoidant, dependent, obsessive-compulsive) assessed via SCID-5-PD
14. Any participant presenting current serious suicide risk, as determined through psychiatric interview, responses to C-SSRS, and clinical judgment of the investigator will be excluded; however, history of suicide attempts is not an exclusion. Any participant who is likely to require hospitalization related to suicidal ideation and behavior, in the judgment of the investigator, will not be enrolled. Any participant presenting with the following on the Baseline C-SSRS will be excluded:
    a. Suicidal ideation score of 4 or greater within the last month of the assessment at a frequency of once a week or more
    b. Suicidal ideation score of 5 within the last 6 months of the assessment
    c. Any suicidal behavior, including suicide attempts or preparatory acts, within the last 6 months of the assessment. Participants with non-suicidal self-injurious behavior may be included if approved by the Medical Monitor
15. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist
16. Require ongoing concomitant therapy with a psychiatric medication with exceptions described in Section 11.0 Concomitant Medications

Medical History

17. Have a history of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure and heart rate. This includes, but is not limited to, a history of myocardial infarction, cerebrovascular accident, or aneurysm. Participants with other mild, stable chronic medical problems may be enrolled if the site physician, CI, and Medical Monitor agree the condition would not significantly increase the risk of MDMA administration or be likely to produce significant symptoms during the study that could interfere with study participation or be confused with side effects of

the IMP. Examples of stable medical conditions that could be allowed include, but are not limited to Diabetes Mellitus (Type 2), Human Immunodeficiency Virus (HIV) infection, Gastroesophageal Reflux Disease (GERD), etc. Any medical disorder judged by the investigator to significantly increase the risk of MDMA administration by any mechanism would require exclusion

18. Have a diagnosis of uncontrolled essential hypertension which is assessed using the recommended criteria of the American Heart Association for Stage 2 hypertension (values of 140/90 milligrams of Mercury [mmHg] or higher assessed on three separate occasions)
19. Have a history of ventricular arrhythmia at any time, other than occasional premature atrial contractions (PACs) or premature ventricular contractions (PVCs) in the absence of ischemic heart disease
20. Have Wolff-Parkinson-White syndrome or any other accessory pathway that has not been successfully eliminated by ablation
21. Have a history of supraventricular arrythmia within the last 12 months. Participants with a history of an allowable supraventricular arrhythmia (see list below) more than 12 months prior to screening and in the absence of any accessory pathway may be enrolled if successfully treated at least 12 months prior and cleared by a cardiologist, the site physician, and Medical Monitor. These arrhythmias may include, and must be limited to, paroxysmal supraventricular tachycardia, paroxysmal atrial tachycardia, or atrial fibrillation that has been successfully treated (e.g., with ablation or cardioversion) at least 12 months previously. Atrial flutter or other arrhythmias will be excluded
22. Have a marked baseline QTcF interval >450 ms demonstrated on repeated ECG assessments. Participants whose QTcF exceeds this value during screening may be initially enrolled if a pre-study concomitant medication is suspected to be prolonging the QT-interval. ECGs should be repeated after initial enrollment and tapering off the pre-study concomitant medication to ensure the participant meets eligibility criteria prior to enrolment confirmation and to IMP dosing.
    - **Note**: The QTcF is the QT interval corrected for heart rate according to Fridericia's formula. It is either machine-read or manually over-read.
23. Have a history of additional risk factors for Torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)
24. Require use of concomitant medications that prolong the QT/QTc interval during Experimental Sessions. Refer to Section 11.0 Concomitant Medications
25. Have symptomatic liver disease or significant liver enzyme elevations
26. Have history of hyponatremia or hyperthermia
27. Weigh less than 48 kilograms (kg)
28. Are pregnant or nursing or are able to become pregnant and are not practicing an effective means of contraception

3.3 Lifestyle Modifications

All participants must agree to the following lifestyle modifications at enrollment and throughout the duration of the study. Participants are eligible to enroll in the study if they:

- Are willing to commit to medication dosing, therapy sessions, follow-up sessions, completing evaluation instruments, and all necessary telephone contact
- Agree to not participate in any other interventional clinical trials during the duration of this study without prior approval of 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 enrollment until their planned course of therapy is complete and an integration period has elapsed

Leading up to Experimental Sessions

- Agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each Experimental Session
- Refrain from the use of any psychoactive medication not approved by the research team from Baseline through Study Termination
- Agree not to use caffeine or nicotine for 2 hours before and at least 6 hours after the initial dose during each Experimental Session
- Are willing to comply with medication requirements per protocol (refer to Section 11.0 Concomitant Medications). 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 Section 11.0 Concomitant Medications), if used for pain management, leading up to the Experimental Session in order to avoid taking the medication 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 or to prevent withdrawal symptoms
- Agree that, for 1 week preceding each Experimental Session, they will refrain from:
  - Taking any herbal supplement (except with prior approval of the research team).
- Agree that, for 5 half-lives of the medication preceding each Experimental Session, they will refrain from:
  - Taking any non-prescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen) 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)

Post Experimental Session

- Are willing to remain overnight at the study site after each Experimental Session until after the Integrative Session the next morning
- Agree to not drive upon completion of each Experimental Session through completion of the Integrative Session the next morning

4.0 Protocol Design

4.1 Proof-of-Principle Therapist Training Lead-In

The Proof-of-Principle lead-in will serve as a training and supervision opportunity for therapy pairs. The sponsor will provide clinical supervision for therapy pairs treating participants. Each new therapy pair participating in the trial will receive clinical supervision at three dedicated time points during treatment of their first subject and additional supervision as needed in subsequent cases. The sponsor's Adherence Raters and trainers will monitor videos of study visits for adherence to the therapeutic method and provide supervision. Participants in the lead-in will be randomized into 2 vs. 3 Experimental Session groups.

4.2 Study Design Overview

This open-label, randomized Phase 2 study will assess the relative safety and effectiveness of two versus three Experimental Sessions of MDMA-assisted therapy in treatment-seeking veterans diagnosed with PTSD.

The study will be conducted in up to 60 participants. Randomization will occur in a 1:1 fashion and will be allocated to Group 1: 3 Experimental Sessions of MDMA-assisted therapy or Group 2: 2 Experimental Sessions of MDMA-assisted therapy.

For each participant, the study will consist of:

- **Screening Period (~4 weeks)**: Phone or in person screen, informed consent, eligibility, and baseline assessment
- **Preparatory Period with Enrollment Confirmation (at least 7 days, max time dependent upon medication tapering)**: medication tapering, Preparatory Sessions and Baseline assessments leading to Enrollment Confirmation.
- **Study Enrollment and Randomization:** Include eligible participants, randomize to group, complete baseline self-report measures, collection of pre-treatment biomarker blood samples
- **Treatment Period (Group 1: 9-15 weeks, Group 2: 6-10 weeks):** Each Experimental Session followed by 3 non-drug Integrative Sessions.
- **Post-treatment (~4 weeks)**: At one-month post final Integrative Session, clinical evaluation and self- report measures, collection of post-treatment biomarker blood samples.
    - For the 2-session group: additional clinical evaluation one month following post-treatment as a secondary outcome.
- **Study Termination:** After the Study Termination visit, participants will have the opportunity to enroll in a separate LTFU study at least six months from the final Experimental Session.

A divided dose of up to 160 mg MDMA, with an initial 120 mg dose, followed by a supplemental dose of 40 mg unless tolerability issues emerge or it is refused by the participant, is administered during the Treatment Period with manualized therapy in two or three open-label monthly Experimental Sessions. Each Experimental Session is followed by three Integrative Sessions of non-drug therapy. Experimental Sessions are followed by an overnight stay. The Primary Outcome measure, the change in CAPS-5 from Baseline, is assessed by a centralized IR pool at one month following the final treatment session (post treatment), and again for the 2 Experimental Session group after a second one-month period (anchored to the date of the baseline CAPS-5). The IR pool will be blinded to treatment assignment, visit number, and number of treatments received, and will not have access to data collected by the sites during the active Treatment Period. Blood samples will be collected at three timepoints: clinical laboratory assessment at Screening to determine eligibility, and biomarker laboratory draws at pre- and post-treatment for future assays. Self-reported PTSD and depression symptoms will be assessed at numerous visits by the PCL-5 and BDI-II, as outlined in Tables 7 and 8.

Figure 1: Study Structure Overview: 2-Session Group

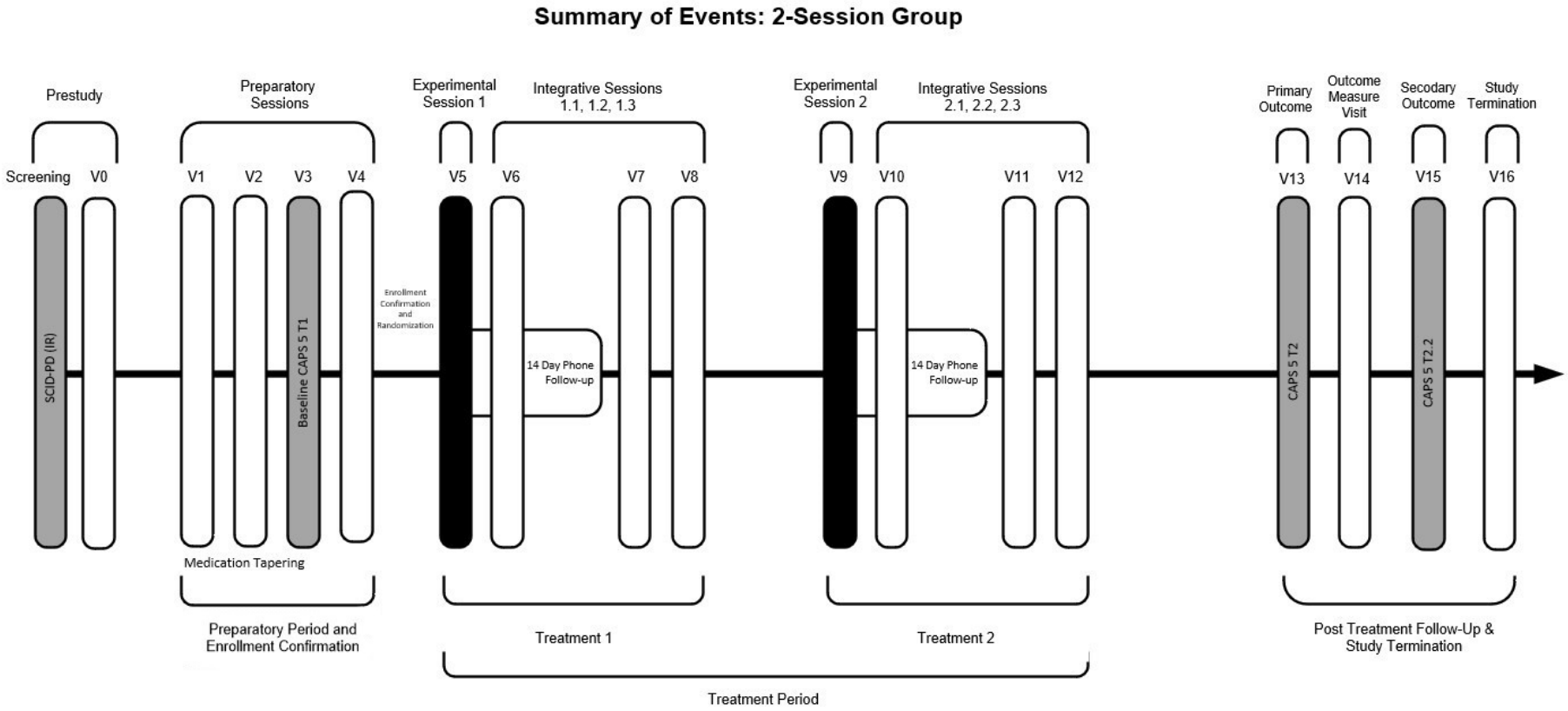
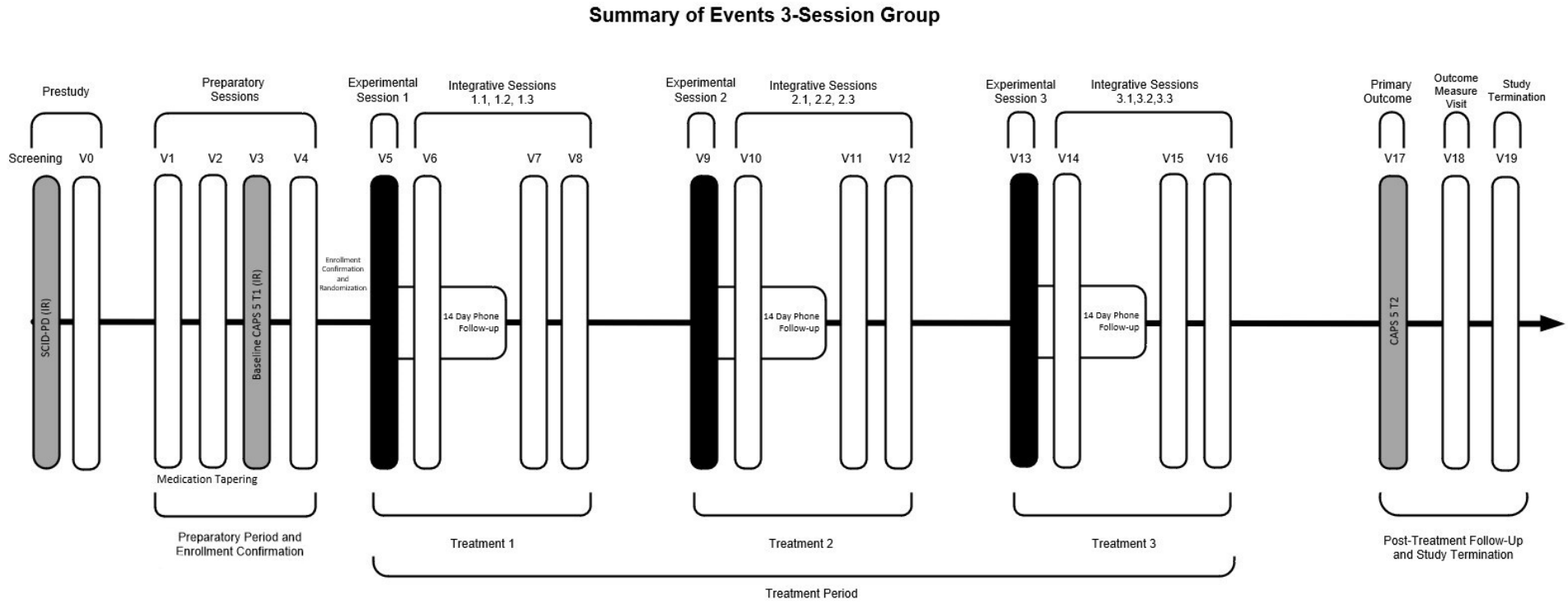


Figure 2: Study Structure Overview: 3-Session Group



Qualified, blinded IRs selected based on availability from the IR Pool will perform the CAPS-5 assessments as described in table below.

Table 1: CAPS-5 Data Collection by Visit

CAPS Number	Visit	Description/Timing	Target Timing Post Baseline
Baseline CAPS-5 T1	V3	Baseline between Visits 2 and 4 (Preparatory Sessions), after medications have been tapered.	Not Applicable
CAPS-5 T2	V13 (2-session group) or V17 (3-session group)	Post Treatment Primary Outcome 49 to 56 days after last Experimental Session	63 to 98 days or 85 to 134 days
CAPS-5 T2.2	V15 *(2-session group only)*	Secondary outcome for 2-session group only 28 to 35 days after T2	85 to 134 days

4.3 Planned Duration of Study

Full screening may take 28 days after completion of initial screening. The Preparatory Period begins at enrollment and can be as brief as 7 days but depending on medication tapering could be as long as necessary to ensure an appropriate medication washout of at least five half-lives of pre-study psychiatric medications and active metabolites, and at least 7 days for stabilization prior to Baseline CAPS-5 T1 (Visit 3). Medication taper for psychological medications should occur prior to Visit 3. Medication taper for medications with drug-drug interactions without a psychological concern should occur prior to Visit 5.

Enrollment confirmation takes place at the completion of the Preparatory Period; at which time the Treatment period will commence. Participant eligibility must be confirmed by the Medical Monitor prior to participant randomization. Treatment begins within 7 days of Baseline CAPS-5 T1 (Visit 3).

The approximately 6 to 15-week treatment period consists of two or three Experimental Sessions 3 to 5 weeks apart with associated non-drug Integrative Sessions. The protocol may remain active up to enrollment of 60 participants. All participants who complete the study will be asked to participate in a LTFU extension study at least 6 months after the last Experimental Session.

After the final Integrative Session 3.3 (Visit 16) or 2.3 (Visit 12) (for the 3 Experimental Session Group and 2 Experimental Session Group, respectively), participants will enter follow-up with no planned study visits for approximately 4 weeks, after which the Primary Outcome CAPS- 5 T2 assessment will take place. Participants in the 2-session group will complete an additional CAPS 5 T2.2 assessment after 4 more weeks. Although there are allowable windows for all visits throughout the protocol, the overall timelines should comply with the target timing of the Primary Outcome CAPS-5 T2 assessment, which must be completed 85 to 134 days post Baseline (3-Session Group) and 63 to 98 days post Baseline (2-Session Group), even if the maximum possible visit windows were used between visits. Other visits should be scheduled to ensure the timing of the Primary Outcome CAPS-5 T2 assessment is appropriate. The Study Termination visit occurs after the final CAPS-5 assessment.

The minimum time that a participant who completes all study visits from Screening to Study Termination will be in the clinical trial is 13 weeks (2-Session Group) or 16 weeks (3-Session Group), and the maximum is dependent on medication tapering. The average participant is expected to complete the study in 20 or 24 weeks (Groups 2 and 1, respectively). Any delays

between visits outside of the protocol-defined windows may result in a corresponding extension of study duration and should be documented as a deviation as appropriate.

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

This clinical trial may be interrupted by the Coronavirus Disease 2019 (COVID-19) global pandemic. Accommodations may be required for study continuation and participant and study site staff safety due to this emergency 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:

- Participants will stay overnight at the study site after each Experimental Session until after the Integrative Session the next morning. The remainder of the Integrative Sessions may be conducted by telemedicine.
- To reinforce the therapeutic alliance between the participant and the therapist pair, all efforts should be reasonably made to conduct Preparatory Sessions (V1, V2, and V4) in person and not via telemedicine.
- Delaying the start of medication tapering after enrollment and the subsequent Treatment Period per Section 11.1 Tapering Instructions
- Delaying Experimental Sessions and associated Integrative Sessions
- Delaying Independent Rater 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 11.0 Concomitant Medications.

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.

4.4 Discontinuation and Completion Criteria

4.4.1 Complete or Evaluable Participants

A participant is considered ‘Evaluable’ and eligible for the mITT analysis if they have completed at least one Experimental Session and one CAPS-5 assessment beyond Baseline.

A participant is considered ‘Evaluable and Completed Per Protocol’ if they have completed all Experimental Sessions and CAPS-5 assessments as planned. These participants will be included in the mITT analysis set and the Per Protocol analysis set.

A participant is considered ‘Evaluable and Early Termination’ if they have completed at least one Experimental Session and one CAPS-5 assessment beyond Baseline but terminated early. These participants will be included in the mITT analysis.

4.4.2 Screen Failures

‘Screen Failures’ are defined as participants who pass phone screening but are deemed ineligible before successfully enrolling in the study at Visit 0. Screen failures may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to Enrollment. All potential participants who begin Screening will be tracked on a Screening Log, and reasons for Screen Failure will be recorded. Screen Failures are not considered evaluable.

Screen Failures may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the participant. Medical assessments may be repeated for confirmation. At any time during Screening, if a potential participant is deemed to be ineligible, classify as a Screen Failure, notify the potential participant that they are unfortunately not eligible for the study, and do not schedule additional Screening assessments. Participants who fail Screening may be rescreened at a later date if deemed appropriate by the investigator but should sign a new copy of the Informed Consent Form (ICF). Screen Failures may request a referral to a VA therapist if eligible and needed. Screen Failures that were scheduled for an IR assessment will be entered into the Electronic Data Capture (EDC) system.

4.4.3 Early Termination from the Study

Participants who are removed from the study after they are randomized and receive IMP but do not complete the study may fall into one of these categories: Post-randomization Early Termination or Dropout. If the participant has received IMP in at least one Experimental Session and completed one CAPS-5 assessment beyond Baseline, they will be considered evaluable. All participants who receive IMP in at least one Experimental Session will be included in all safety analyses.

Participants can withdraw from treatment or withdraw consent at any time for any reason without judgment. The site team can withdraw a participant if, in their clinical judgment, it is in the best interest of the participant or if the participant cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If the site team makes the decision to terminate the participant from treatment or the study, they will explain the reason for withdrawal and document in the participant's source records and eCRF. If a participant develops any Exclusion Criteria that, in the opinion of the Medical Monitor or Site, affects the safety of the participant, including psychiatric diagnosis, medical diagnosis, pregnancy, or requiring use of prohibited medications, the participant will discontinue treatment in Experimental Sessions but remain in the study for the associated Integrative Sessions. Participants whose Experimental Sessions are delayed by the COVID-19 pandemic may start any of these medications during the delay, as clinically indicated. When study visits resume, they will be given the option to resume Experimental Sessions after tapering off of these medications per Section 11.1 Tapering Instructions. Any time a participant terminates from the study early, the site team will attempt to obtain information about AE outcomes if appropriate, as determined by the site physician and Medical Monitor. The site team will provide the participant with a Post-Study Plan as described in Section 7.4.3 Post-Study Plan.

- **Post-randomization Early Termination**: Participants who discontinue study treatment but continue to participate in Independent Rater primary and secondary outcome assessments. Data collection by IRs will continue on the same schedule as planned through Study Termination visit procedures.
- **Dropout**: If a participant decides to withdraw consent completely, they will terminate without further follow-up. If the participant agrees, they will complete a final CAPS-5 assessment. These participants are defined as dropouts who withdraw consent due to any reason after receiving at least one dose of IMP and no longer participate in the study (i.e., no further contact with investigators or site staff). Data collected on study participants up to the time of withdrawal of consent will remain in the trial database in order to maintain scientific validity. Removal of data from the database would undermine the scientific and ethical integrity of the research.

4.4.4 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to attend scheduled visits and are unable to be contacted by the site staff. If the participant has completed at least one Experimental Session and one CAPS-5 assessment beyond Baseline, they will be considered evaluable. All participants with at least one Experimental Session will be included in the safety analysis.

If a participant does not attend a scheduled visit, the site must attempt to contact the participant to reschedule the visit as soon as possible and emphasize the importance of complying with the protocol specified visit schedule. The staff should determine if the participant is willing to comply with future visits.

If a participant does not respond to this initial contact, the site staff must make multiple efforts to contact the study participant and document each attempt in the source record. At least three attempts should be made via telephone, over the course of approximately 7 days, with calls at different times of day. If telephone contact fails, an email should be sent if such contact information was provided. The emergency contact the participant provided should be contacted and asked to attempt contact with the participant. Lastly, a certified letter (or equivalent) should be sent to their last known mailing address. If the participant fails to respond to all of these contacts, they will be considered to have withdrawn from the study and are lost to follow-up.

4.5 End of Study Definition and Premature Discontinuation

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in Table 4: Time and Events-Study Procedures-Pre-Treatment (All Groups) for the last participant in the trial globally.

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 a Post-Study Plan. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with federal and state regulations.

4.6 Rationale of Dose Selection

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 75, 100 and 125 mg MDMA initial doses with the supplemental dose are active and effective in two to three Experimental Sessions. MDMA doses with an optimal risk-benefit ratio range from 75 mg (Cohen's d Independent Groups Pre-test Post-test [dIGPP]=2.73, N=7) to 125 mg (Cohen's dIGPP=0.77, N=58) initial dose of MDMA with a 2-session treatment package. In Phase 2 studies, the sponsor observed a -36.4-point mean change in CAPS-4 scores among active dose participants receiving two Experimental Sessions (N=72) compared to a -44.2 point mean change after three Experimental Sessions (N=51). Although uncontrolled, the additional 7.8 point mean reduction observed after three Experimental Sessions compared to two, along with the observed favorable safety profile formed the basis for comparing a 2- versus 3-session treatment package. Larger doses have been administered safely in MP2 (150 mg and 75 mg supplemental) and in Phase 1 studies (150 mg and 160 mg). The results of these Phase 2 studies led to the selection of 80 mg and 120 mg MDMA as the initial active doses to be compared to inactive placebo in Phase 3 trials.

This open-label study will compare the effects of initial doses of 120 mg MDMA administered in two versus three Experimental Sessions. Initial doses per Experimental Session are 120 mg of MDMA compounded with inactive excipients, followed 1.5 to 2 hours later by a supplemental

dose of 40 mg unless tolerability issues emerge with the first dose or it is refused by the participant. The initial active doses of 120 mg are expected to produce all commonly reported effects of MDMA. The supplemental dose will prolong subjective effects of MDMA without producing physiological effects much greater than peak effects occurring after the initial dose and will be administered unless tolerability issues emerge with the first dose or it is refused by the participant. Total amounts of MDMA to be administered per Experimental Session range from 120 mg to 160 mg.

Table 2: Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	120 mg	40 mg	120 mg to 160 mg
2	120 mg	40 mg	120 mg to 160 mg
3	120 mg	40 mg	120 mg to 160 mg
Total Cumulative Dose: 2 Session Group			240 mg to 320 mg
Total Cumulative Dose: 3 Session Group			360 mg to 480 mg

***** Unless tolerability issues emerge with the first dose or it is refused by the participant. Supplemental dose will be 40 mg for all subjects throughout the study.

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 with the first dose or it is refused by the participant.

5.0 Therapy

5.1 Description of Therapeutic Method

The largely non-directive therapeutic method of MDMA-assisted therapy is described in detail in the Treatment Manual. All therapy pairs will be extensively trained in a multi-week 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.

5.2 Therapy Pair Qualifications

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

- One or more two-person therapy pairs will be on the study team, who have been reviewed and approved by the MDMA Therapy Training Program.
- One person per therapy pair is required to be licensed to provide therapy according to state or province and local requirements.
- If one person in the therapy pair 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-therapy pair.

A physician will be required to be on the study team, and to be on-site for the duration of Experimental Sessions, to assess participant safety. Each site will also be required to have one person licensed to manage and administer controlled substances.

5.3 Training

The sponsor's 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 an online training module, and participating in an in-person or online training program that includes watching and discussing videos of Experimental Sessions. The final part of training includes supervision provided by the sponsor at three dedicated time points during treatment of each therapy team member's first subject, and additionally as needed in subsequent cases. 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.

5.4 Adherence to Therapeutic Method

Therapy sessions, including Experimental Sessions, may be recorded, with recordings preserved for research and training purposes. Adherence criteria and competence ratings will be conducted by qualified, trained, and blinded Adherence Raters who will analyze video data from specific and randomly selected Preparatory Sessions, Experimental Sessions, and Integrative Sessions. The elements included in adherence criteria are specific to each type of session and are defined in the Treatment Manual. These ratings will be collected, at minimum, for each therapy pair in the study. Ratings will be used to provide feedback to new therapy pairs, to further characterize the manualized therapy, and for future exploratory research.

6.0 Measures and Reliability

The following eligibility, outcome, exploratory, and safety measures will be used in the study, in accordance with Table 7: Time and Events-Study Measures- Group 1 (3 experimental sessions) and Table 8: Time and Events-Study Measures- Group 2 (2 experimental sessions).

Table 3: Protocol Objectives and Assessment Tools

Objectives	Measure	Measure Type	Administration
Eligibility			
Assess psychiatric disorders	MINI	Eligibility	Telemedicine (IR)
Assess personality disorders	SCID-5-PD with SCID-5-SPQ	Eligibility	Telemedicine (IR)/self-report measures at Site
Assess PTSD symptom severity	PCL-5 with LEC-5	Eligibility	Site
Identify dissociative disorders	DDIS	Eligibility	Telemedicine (IR)
Confirm PTSD diagnosis and symptom severity	CAPS-5	Eligibility	Telemedicine (IR)
Primary			

Assess changes in PTSD symptom severity from Baseline to Visit 13 (2-Session Group) or Visit 17 (3-Session Group) compared between groups	CAPS-5	Outcome	Telemedicine (IR)
Secondary			
Assess changes in clinician-rated functional impairment from Baseline to Visit 13 (2-Session Group) or Visit 17 (3-Session Group) compared between groups	SDS	Outcome	Telemedicine (IR)
Assess changes in PTSD symptom severity from Baseline to Visit 15 (2-Session Group only)	CAPS-5	Outcome	Telemedicine (IR)
Exploratory			
Explore changes in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal as measured by changes in CAPS-5 subscale scores	CAPS-5	Outcome	Telemedicine (IR)
Characterization of PTSD severity and cluster scores collected prior to each session to explore onset of treatment effectiveness with a descriptive time course plot	PCL-5	Outcome	Site
Assess changes in severity of dissociative symptoms associated with PTSD from Baseline to Visit 13 (2-Session Group) or Visit 17 (3-Session Group) compared between groups	DSP-I	Outcome	Telemedicine (IR)
Explore correlation of dissociative symptoms associated with PTSD with theCAPS-5 Total Severity analyses	DSP-I CAPS-5	Outcome	Telemedicine (IR)
Explore the effect of adverse childhood experiences on PTSD treatment outcomesas a covariate on the CAPS-5 Total Severity analyses	ACE CAPS-5	Outcome	Site
Explore the effect of combat experienceson PTSD treatment outcomes as a covariate on the CAPS-5 Total Severity analyses	DRRI-2 CAPS-5	Outcome	Site
Assess changes in depression symptoms from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	BDI-II	Outcome	Site
Assess changes in chronic pain from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	CPGS	Outcome	Site
Assess changes in Moral Injury from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	MIES	Outcome	Site
Assess changes in Posttraumatic Growth from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	PTGI	Outcome	Site

Assess changes in self-compassion from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	SCS	Outcome	Site
Assess changes in anger from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	BPAQ-SF	Outcome	Site
Assess changes in experiential avoidance and acceptance from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	AAQ-II	Outcome	Site
Assess changes in alcohol use from Screening to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	AUDIT	Healthcare cost	Site
Assess changes in drug use from Screening to Visit 14 (2-Session Group) or Visit 18 (3-Session Group)	DUDIT	Healthcare cost	Site
Assess facility-based healthcare utilization at Screening	UFEC	Healthcare cost	Site
Assess changes in clinician-rated functional impairment from Visit 4 to Visit 14 (2-Session Group) or Visit 18 (3-Session Group) compared between groups	WHOQOL-BREF	Outcome	Site
Assess the effects of traumatic brain injury on PTSD treatment outcomes as a covariate on the CAPS-5 Total Severity Analyses	OSU-TBI CAPS-5	Outcome	Site
Assess incidence of positive or serious ideation and suicidal behavior	MAPS-Adapted C-SSRS	Safety and Outcome	Site

6.1 Primary Outcome Measure and Reliability

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

The last month CAPS-5 is a semi-structured interview that assesses index history of DSM-5-defined traumatic event exposure [70], including the most distressing event, time since exposure, to produce a diagnostic score (presence vs. absence) and a PTSD Total Severity score [70]. 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 CAPS-5 will be administered by a blinded IR via telemedicine. 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. 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, which strengthens the study blind.

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, treatment assignment, and any study data for the participant. IR visits will be assigned based on availability.

6.2 Secondary Measure

6.2.1 SDS (Sheehan Disability Scale) for PTSD for MAPS

The SDS is a clinician-rated assessment of functional impairment [71]. The SDS has high internal consistency and accurately identified 80% of a sample of primary care patients with mental disorders [72]. The Customized version of the SDS for PTSD for the MAPS studies 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 an eleven-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 MAPS takes 5 minutes to complete.

Administration and reliability of SDS for PTSD for MAPS: 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 Independent Rater Pool.

6.3 Screening Measures and Reliability

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

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [73]. 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 assesses the experience of the participant with suicidal ideation and behavior over their lifetime and within 6 months prior to entry into the trial and will be completed for all potential participants at screening to determine eligibility. All subsequent administrations will utilize the Since Last Visit version to assure that the participant continues to qualify for the trial. 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 for Lifetime obtained a Cronbach’s alpha of 0.93 and 0.94 for the Since Last Visit form, and Last Visit C-SSRS severity scores were positively correlated with the BDI “suicide thoughts” item [74]. This study will utilize the MAPS-adapted versions of the Baseline/Screening and Since Last Visit C-SSRS measures. 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. Kelly Posner for use in MAPS Research.

6.3.2 MINI (Mini-International Neuropsychiatric Interview)

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 [75], is now compatible with DSM-5 and will be administered by a member of the Independent Rater Pool to screen for psychiatric conditions per DSM-5. 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 [76]. The MINI takes between 15 and 20 minutes to perform and addresses major psychiatric disorders. 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 [76, 77]. Testing on nonpsychiatric samples did not create false positives [75].

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

The SCID-5-PD will be administered by a blinded IR via telemedicine [78]. Prior to the SCID-5-PD clinical interview, participants will complete a brief self-report questionnaire called the SCID-5 Self-report Personality Questionnaire (SCID-5-SPQ) as a self-report screening tool used to assess for personality disorders. Potential personality disorders that satisfy diagnostic thresholds will be further assessed via clinical interview during the SCID-5-PD. IRs will receive training on administering these measures from a research reliable trainer. Interviews may be recorded in as many instances as necessary to establish reliability of a random selection of interviews for accuracy.

6.3.4 LEC-5 (Life Events Checklist for DSM-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 [79].

6.3.5 PCL-5 (PTSD Checklist)

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 [80]. 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 five-point Likert-type scale (1=Not at all to 5=Extremely). A total PCL-5 score of 36 or greater at Screening will be required for initial enrollment.

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

Questions on the DDIS specifically addressing dissociative disorder symptoms (items 117-130) will be asked by an IR during Screening. 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 [81].

Owing to overlap with items found between the DDIS and other screening measures, only questions specifically addressing DID will be assessed.

6.4 Exploratory Measures

6.4.1 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 and recommended for use as an additional or complementary measure ("add-on") to the CAPS-5 [82]. 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 [83-85]. The DSP-I takes approximately 5 to 15 minutes to complete. It consists of two parts, 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 was first developed in 2016 and revised in 2017.

6.4.2 ACE (Adverse Childhood Experience Questionnaire)

The ACE is a 10-item checklist measure assessing number and types of adverse childhood experiences, including neglect and emotional, physical, and sexual abuse. Respondents are asked if an experience happened "often" and if so, to write "1". The total score reflects the number of adverse childhood experiences. The measure was first used in the context of a study investigating the relationship between childhood adverse experiences and health outcomes in adulthood [86] 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[87-90]. The scoring method has been used in archival research, finding an association between increased scores and health problems in several generations [89].

6.4.3 BDI-II (Beck Depression Inventory II)

The BDI-II is a revision of the BDI, a 21-item self-report measure [91, 92] that will serve as a measure of depression symptom severity [93]. 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. It takes 5 to 10 minutes to complete [93]. 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 [93, 94]. Higher scores indicate more severe depressive symptoms.

6.4.4 CPGS (Chronic Pain Grade Scale)

The CPGS is a seven-item measure of pain. Responses to six of the seven items are made on a 10-point Likert scale, and a response on the other item is the number of days in the past 3 to 6 months when pain prevented the respondent from carrying out everyday activities [95]. Responses to questions are used to attain a rating (grade) for pain from 0 (no pain) to five (high disability, severely limiting). The instrument has three scale scores: pain severity, pain intensity, and pain-related disability. Estimated time to complete is 3 to 5 minutes. The CPGS is a validated

scale with high internal consistency (Cronbach's alpha = 0.90) and correlated with other instruments assessing pain [96].

6.4.5 SCS (Self-Compassion Scale)

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 [97]. Respondents complete the SCS by indicating how typical they feel on each item on a five-point Likert scale (1=Almost never and 5=Almost always). It is estimated to take between 4 to 8 minutes to complete. 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 [98].

6.4.6 AUDIT (Alcohol Use Disorders Identification Test)

The AUDIT is a ten-item self-report test. Respondents answer on a 5-point scale (0=Never or none, 4=Daily or greatest number) [99]. The ninth item addresses occurrence of injury of self or other as a result of drinking and the tenth addresses others' concerns about the respondent's drinking, with only three responses provided (0=No, 2=Yes, but not during the last year, 3=Yes, during the last year). The measure can readily detect alcohol abuse disorders in a wide array of individuals [100].

6.4.7 DUDIT (Drug Use Disorders Identification Test)

The DUDIT is an 11-item measure designed to assess presence of substance use disorders [101]. Responses to items are made on a 5-point scale with exact responses varying across questions. When present, use can be described in monthly or less than monthly versus four times a week or daily. A list of substances is provided at the end of the measure. The DUDIT is reliable, with a Cronbach's alpha of 0.80. When compared with an interview based on ICD 10, the DUDIT had a sensitivity to detecting substance use disorders of 90% and a specificity of 80% [101]. The English translation was developed from a Swedish-language original. Estimated time to complete is 2 to 4 minutes.

6.4.8 MIES (Moral Injury Event Scale)

The MIES is a 9-item Likert-type scale assessing the experience and impact of potentially morally injurious events. The MIES is comprised of two underlying latent factors: Perceived Transgressions and Perceived Betrayals. The MIES has good internal validity and temporal stability [102].

6.4.9 PTGI (Posttraumatic Growth Inventory)

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 [103]. 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 [103, 104].

6.4.10 BPAQ-SF (Buss Perry Aggression Questionnaire Short Form)

The BPAQ-SF is a well-validated and widely used 12 item scale with four factors: Physical Aggression, Verbal Aggression, Anger, and Hostility [105].

6.4.11 AAQ-II (Acceptance and Action Questionnaire)

The AAQ-II is a 7-item, self-rated measure that assesses the construct variously described as acceptance, experiential avoidance, and psychological flexibility. The measure has demonstrated good reliability and validity, and the AAQ-II has shown concurrent and predictive associations with a range of mental health and functional outcomes [106].

6.4.12 WHOQOL-BREF (WHO Quality of Life-BREF)

The World Health Organization Quality of Life (WHOQOL) project was initiated in 1991. The aim was to develop an international cross-culturally comparable quality of life assessment instrument [107, 108]. It assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards, and concerns. The WHOQOL instruments were developed collaboratively in a number of centers worldwide and have been widely field-tested.

The WHOQOL-BREF instrument comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment. The WHOQOL-BREF was derived from data collected using the WHOQOL-100. It produces scores for four domains related to quality of life: physical health, psychological, social relationships, and environment. It also includes one facet on overall quality of life and general health.

6.4.13 DRRI-II (Deployment Risk and Resilience Inventory-2)

The DRRI, developed by the VA National Center for PTSD, is a suite of scales that assess key deployment-related risk and resilience factors with demonstrated implications for Veterans' long-term health [109]. Scales D (combat experiences) and E (post-battle experiences) will be administered.

6.4.14 UFEC (Utilization of Facility-based and Emergent Care)

The UFEC is a sponsor-developed measure assessing participant health events, including hospitalization and use of healthcare facilities, including in-patient hospitalization, rehabilitation facilities and other health care facilities for a set period prior to study entry.

6.4.15 OSU-TBI-ID (Ohio State University Traumatic Brain Injury Identification Method)

The OSU TBI-ID is a standardized assessment for eliciting lifetime history of TBI via a structured interview [110].

7.0 Study Procedures

All assessments must be performed by qualified study staff delegated these duties on the Site Responsibilities Log. 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.

Table 4: Time and Events-Study Procedures-Pre-Treatment (All Groups)

	Screening and Enrollment Period (~4 weeks, +/- 2 weeks)				**Preparatory Period with Enrollment Confirmation** At least 7 days, depending on medication tapering plan			
	Screening			**Enrollment**	**Preparatory**		**Baseline CAPS-5 T1**	**Baseline & Enrollment Confirmation**
Visit	Phone/in-person Screening	Screening	IR Evaluation	V0	V1	V2	V3	V4
Visit Description	Phone/in person	In-person Visits & Labs	Telemedicine	Enrollment	Prep. 1	Prep. 2	Telemedicine	Prep. 3 & Enrollment Confirmation
Visit Timing	Prior to Initial Screening	Over 7 to 28 days	2 to 9 days after initial eligibility met	2 to 14 days post IRScreening	0 to 12 days after V0	At least 2 days after V1 (depending on Medication tapering)	Post V2 & Taper (Confirmed by Phone call)	3 to 6 days After V3
Initial Phone Screen	S #							
Informed Consent	Send or provide copy	S #						
Follow-up Phone Screen	S #							
Assess Eligibility	S #	S #		S #	S #	S #		S #
Medical/Psychiatric History	S [A]	S #		S #	S #	S #		S #
Past/Current Medication & Adherence	S #	S #		S #	S #	S #		S #
Weight, BP, Pulse, Temperature		S #						
Physical Exam		S #						
ECG & Rhythm Strip		S #						
Clinical Lab Tests		S #						
Drug Screen		S #		#				
Pregnancy Screen [G]		S #		#				
Biomarker Blood Sample								S [D]
Enter Participant in eCRF [B]		S #						
Record			S #	#	S #	S #	S #	S #
Study Enrollment				S [E]				S Confirmed
Medication Taper				S #	S #	S #		
All AEs [C]				S #	S #	S #		S #
90-min Preparatory Session				#	S #	S #		S #
Phone Call Follow-up [F]						S #		S #

[A] At Screening, collect data on previous hospitalizations and healthcare utilization. Request participants to obtain medical/psychiatric records to bring to the in-person screening.
[B] Participants will be entered into the eCRF after the IR visit is scheduled
[C] All Adverse Events (AEs) includes collecting Serious Adverse Events, AEs of Special Interest, AEs of Psychiatric Status, AEs requiring medical advice or attention, AEs that indicate withdrawal of a participant, and allother AEs
[D] Blood samples will be drawn from participants at two time points (pre- and post-treatment) in order to bank samples for future assay. Pre-Treatment blood draw will occur after V3 and before V5.
[E] Enrollment eligibility must be confirmed by the Medical Monitor prior to participant randomization
[F] If needed, call participant to confirm medication tapering and stabilization is complete prior to Visit 3
[G] For people able to become pregnant (PABP) only

Table 5: Treatment Period, Follow-Up, and Study Termination-Group 1 (3 Experimental Sessions)

	Treatment Period: Group 1 (3 Experimental Sessions) ~9-15 weeks												**Post-Treatment Period** (~5 weeks)		
	Treatment 1				**Treatment 2**				**Treatment 3**				**Primary Outcome**	**Outcome Site Visit**	**Study Termination**
Visit	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19
Visit Description	Exp.1	Int. 1.1	Int. 1.2	Int. 1.3	Exp. 2	Int. 2.1	Int. 2.2	Int. 2.3	Exp. 3	Int. 3.1	Int. 3.2	Int. 3.3	CAPS-5 T2 Outcome: Tele-medicine [A]	Outcome Site Visit	Study Termination
Visit Timing	Within 7 days after V3	Morn-ing after V5	~1 week (3 to 14 days) after V5	~2 weeks (10 to 21 days) after V5	~3 weeks (21 to 35 days) after V5	Morn-ing after V9	~1 week (3 to 14 days) after V9	~2 weeks (10 to 21 days) afterV9	~3 weeks (21 to 35 days) after V9	Morn-ing after V13	~1 week (3 to 14 days) after V13	~2 weeks (10 to 21 days) after V13	85 to 134 days after V3; ~ 7 weeks after V13	2 days (1 to 7 days) after V17	~2 days (0 to 7 days) after V18
Past/Current Medication & Adherence	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #		S #	S #
Drug Screen	S #				S #				S #						
Pregnancy Screen [B]	S #				S #				S #						
Biomarker Blood Sample													S [C]		
Record	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #		
All AEs [D]	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #	S #		S #	S #
Randomization [E]	S #														
Administer IMP	S #				S #				S #						
8-hour Exp. Session	S #				S #				S #						
BP, Pulse, Temp. [F]	S #				S #				S #						S [G]
Overnight Stay	S #				S #				S #						
90-min Integrative Session		S #	S #	S #		S #	S #	S #		S #	S #	S #			
Phone Call Follow-up [H]		S #				S #				S #					
Weight														#	S #

[A] All visits must be scheduled to ensure that the Primary Outcome CAPS-5 T2 assessment is within the overall window provided.
[B] For people able to become pregnant (PABP) only
[C] Blood samples will be drawn from participants at two time points (pre- and post-treatment) in order to bank samples for future assay.
[D] All Adverse Events (AEs) includes collecting Serious Adverse Events, Aes of Special Interest, Aes of Psychiatric Status, Aes requiring medical advice or attention, Aes that indicate withdrawal of a participant, and all other Aes
[E] Randomize 24 to 48 hours prior to first Experimental Session
[F] During Experimental Sessions, vitals are measured before Investigational Product administration, immediately before the supplemental dose is administered (or would be, if supplemental dose not given), and approximately 6 to 8 hours after initial dose, and as needed
[G] At Study Termination, only blood pressure needs to be measured
[H] 14 days of phone follow-up, with one phone call every other day starting 2 days after the Experimental Session

Table 6: Treatment Period, Follow-Up, and Study Termination-Group 2 (2 Experimental Sessions)

	Treatment Period: Group 2 (2 Experimental Sessions) ~6-10 weeks								**Post-Treatment Period** (~9 weeks)			
	Treatment 1				**Treatment 2**				**Primary Outcome**	**Outcome Site Visit**	**Secondary Outcome**	**Study Termination**
Visit	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Visit Description	Exp. 1	Int. 1.1	Int. 1.2	Int. 1.3 [G]	Exp. 2	Int. 2.1	Int. 2.2	Int. 2.3	CAPS-5 T2 Outcome: Tele-medicine [A]	Outcome Site Visit	CAPS-5 T2.2 Outcome: Tele-medicine	Study Termination
Visit Timing	Within 7 days after V3	Morning after V5	~1 week (3 to 14 days) after V5	~2 weeks (10 to 21 days) after V5	~3 weeks (21 to 35 days) after V5	Morning after V9	~1 week (3 to 14 days) after V9	~2 weeks (10 to 21 days) after V9	63 to 98 days after V3; ~ 7 weeks after V9	2 days (1 to 7 days) after V13	85 to 134 days after V3	~2 days (1 to 7 days) post V15
Past/Current Medication & Adherence	S #	S #	S #	S #	S #	S #	S #	S #		S #	S #	S #
Drug Screen	S #				S #							
Pregnancy Screen [B]	S #				S #							
Biomarker Blood Sample									S [C]			
Record	S #	S #	S #	S #	S #	S #	S #	S #	S #			
All Aes [D]	S #	S #	S #	S #	S #	S #	S #	S #		S #	S #	S #
Randomization [E]	S #											
Administer IMP	S #				S #							
8-hour Exp.Session	S #				S #							
BP, Pulse, Temperature [F]	S #				S #							S [G]
Overnight Stay	S #				S #							
90-min IntegrativeSession		S #	S #	S #		S #	S #	S #				
Phone Call Follow-up [H]		S #				S #						
Weight												S #

[A] All visits must be scheduled to ensure that the Primary Outcome CAPS-5 T2 assessment is within the overall window provided.
[B] For people able to become pregnant (PABP) only
[C] Blood samples will be drawn from participants at two time points (pre- and post-treatment) in order to bank samples for future assay. Post-treatment blood draw will occur within 9 days of V13.
[D] All Adverse Events (Aes) includes collecting Serious Adverse Events, Aes of Special Interest, Aes of Psychiatric Status, Aes requiring medical advice or attention, Aes that indicate withdrawal of a participant, and all other Aes
[E] Randomize 24 to 48 hours prior to first Experimental Session
[F] During Experimental Sessions, vitals are measured before Investigational Product administration, immediately before the supplemental dose is administered (or would be, if supplemental dose not given), and approximately 6 to 8 hours after initial dose, and as needed
[G] At Study Termination, only blood pressure needs to be measured
[H] 14 days of phone follow-up, with one phone call every other day starting 2 days after the Experimental Session

Table 7: Time and Events-Study Measures-Group 1 (3 Experimental Sessions)

	Screening				Baseline & Enrollment Confirmation		Treatment 1			Treatment 2			Treatment 3			Post-Treatment Follow-Up& Study Termination		
	Visit #	Site [A]	IR Screening	V0	V3	V4	V5	V6 & 7	V8	V9	V10 & 11	V12	V13	V14 & 15	V16	V17	V18	V19
Visit Description	**~Time to Complete Measure (minutes)**	Site Visit	Tele-medicine	Site visit	Baseline CAPS-5 T1	Prep. 3 & Enrollment Confirmation	Exp. 1	Int. 1.1 & 1.2	Int. 1.3	Exp. 2	Int. 2.1 & 2.2	Int. 2.3	Exp. 3	Int. 3.1 & 3.2	Int. 33	CAPS-5 T2 Outcome: Telemedicine	Outcome Site Visit	Study Termination
CAPS-5	90 (Baseline) 60 (all others)				✓											S #		
SDS	5				✓											✓		
DSP-I	15				✓											✓		
MINI	15		✓															
SCID-5-PD	60		✓															
SCID-5-SPQ	20	✓																
WHOQOL-BREF	10					✓											✓	
AAQ-II	3					✓											✓	
C-SSRS [B]	10	✓	✓	✓#	#	S	S [C]	S #	S #	S [C]	S #	S #	S [C]	S #	S #	#	S #	S #
SCS	6					✓											✓	
DDIS [D]	5		✓															
BPAQ-SF	12					✓											✓	
DRRI-II [E]	11			✓														
LEC-5	5	✓																
PCL-5	8	✓					S [F]			S [F]			S [F]				✓	
MIES	4					✓											✓	
ACE	4			✓														
BDI-II	10 (Baseline) 5 (all others)						✓[G]			✓[G]			✓[G]				✓	
CPGS	5					✓											✓	
PTGI	8					✓											✓	
OSU-TBI	5			✓														
UFEC	3			✓													✓	
AUDIT	3	✓															✓	
DUDIT	3	✓															✓	
~Total Time of Completing Measures (minutes)		**49**	**90**	**23**	**110**	**76**	**23**	**10**	**10**	**23**	**10**	**10**	**23**	**10**	**10**	**80**	**80**	**80**

[A] Ensure that LEC-5 and SCID-5-SPQ results are sent to the Independent Rater who will be conducting the SCID-5-PD
[B] First C-SSRS is a Baseline/Screening assessment, other assessments are Since Last Visit Additional C-SSRS measures may be conducted as clinically indicated. The site will utilize the MAPS-adapted C-SSRS.
[C] Conducted pre- and post-IMP administration, and at phone calls every other day for 14 days starting 2 days after Experimental Session
[D] The relevant questions (117-130) from the DDIS will be asked by the Independent Rater during the SCID-5-PD assessment. The entire measure will never be administered.
[E] Only scales D (combat experiences) and E (post-battle experiences) of the DRRI-II will be administered.
[F] PCL-5 conducted pre-IMP administration.
[G] BDI-II conducted pre-IMP administration.

Table 8: Time and Events-Study Measures-Group 2 (2 Experimental Sessions)

	Screening				Baseline & Enrollment Confirmation		Treatment 1			Treatment 2			Post-Treatment Follow-Up & Study Termination			
	Visit #	Site [A]	IR Screening	V0	V3	V4	V5	V6 & 7	V8	V9	V10 & 11	V12	V13	V14	V15	V16
Visit Description	**~Time to Complete Measure (minutes)**	Site Visit	Tele-medicine	Site Visit	Baseline CAPS-5 T1	Prep. 3 & Enrollment Confirmation	Exp. 1	Int. 1.1 & 1.2	Int. 1.3	Exp. 2	Int. 2.1 & 2.2	Int. 2.3	CAPS-5 T2 Outcome: Telemedicine	Outcome Site Visit	CAPS-5 T2.2: Outcome: Telemedicine	Study Termination
CAPS-5	90 (Baseline) 60 (all others)				✓								S #	#	S #	
SDS	5				✓								✓		✓	
DSP-I	15				✓								✓		✓	
MINI	15		✓													
SCID-5-PD	60		✓													
SCID-5-SPQ	20	✓														
WHOQOL-BREF	10					✓								✓		
AAQ-II	3					✓								✓		
C-SSRS [B]	10	✓	✓	✓#	#	S	S [C]	S #	S #	S [C]	S #	S #	#	S #	#	S #
SCS	6					✓								✓		
DDIS [D]	5		✓													
BPAQ-SF	12					✓								✓		
DRRI-II [E]	11			✓												
LEC-5	5	✓														
PCL-5	8	✓					S [F]			S [F]				✓		✓
MIES	4					✓								✓		
ACE	4			✓												
BDI-II	10 (Baseline) 5 (all others)						✓[G]			✓[G]				✓		✓
CPGS	5					✓								✓		
PTGI	8					✓								✓		
OSU-TBI	5			✓												
UFEC	3			✓										✓		
AUDIT	3	✓												✓		
DUDIT	3	✓												✓		
~Total Time of Completing Measures (minutes)		**49**	**90**	**23**	**100**	**76**	**23**	**10**	**10**	**23**	**10**	**10**	**80**	**80**	**80**	**23**

[A] Ensure that LEC-5 and SCID-5-SPQ results are sent to the Independent Rater who will be conducting the SCID-5-PD.
[B] First C-SSRS is a Baseline/Screening assessment, other assessments are Since Last Visit. Additional C-SSRS measures may be conducted as clinically indicated. The site will use the MAPS-adapted C-SSRS.
[C] Conducted pre- and post-IMP administration, and at phone calls every other day for 14 days starting 2 days after Experimental Session.
[D] The relevant questions (117-130) from the DDIS will be asked by the Independent Rater during the SCID-5-PD assessment. The entire measure will never be administered.
[E] Only scales D (combat experiences) and E (post-battle experiences) of the DRRI-II will be administered.
[F] PCL-5 should be conducted pre-IMP administration.
[G] BDI-II should be conducted pre-IMP administration.

7.1 Screening and Enrollment Period

7.1.1 Screening

Prospective participants will be pre-screened in person or by telephone according to an IRB-approved script to ascertain if they meet basic eligibility criteria. All individuals who are pre-screened should be assigned a Screening Number and recorded on the Screening Log. 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. 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.

If deemed potentially eligible, the potential participant will receive a copy of the ICF for review and invited to begin screening. Relevant medical and psychiatric records are required for the site physician to obtain a well-characterized medical history and assess eligibility. The physician may need to contact the prescribing physician to discuss the tapering of medications (see Section 11.0 Concomitant Medications).

Site staff (preferably the therapy pair who would be treating this potential participant) will explain and obtain written 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 will take place over multiple visits and will be completed in-person, via telemedicine, or over the telephone. All procedures must be completed but there can be some flexibility in timing and order of individual assessments within the Initial Eligibility and Medical Assessments categories below:

- Initial Eligibility, including measures, in-person discussions, and review of medical records
- Medical Assessments, including labs, electrocardiogram (ECG), and physical exam
- The site staff will schedule the IR assessment and send IR the results of initial measures The sponsor recommends the following order of assessments:

Initial Eligibility
Qualified site staff will:

- Review medical and psychiatric history with the participant via interview and review of provided records. If no records were provided or those provided are not sufficient, request additional records. Collect data on previous hospitalizations and healthcare utilization.
- Support the participant during completion of the LEC-5 with PCL-5 to confirm PTSD diagnosis and severity. Support is needed to ensure proper identification of the index trauma on the PCL-5. Symptom severity is assessed in relation to the index trauma.
- Administer the Baseline/Screening C-SSRS to assess history of suicidal behavior and ideation.
- Review past and current medications and adherence to prescriptions.

- Assess ability to become pregnant and discuss requirement for commitment to adequate contraception for the duration of the study. Perform urine pregnancy test for participants who are of able to become pregnant.
- Perform a urine drug test.
- Direct participant to complete self-reported Screening measures:
    - SCID-5-SPQ
    - AUDIT
    - DUDIT
    - PCL-5
    - LEC-5
- Review results of all measures and discussions against eligibility criteria to assess initial eligibility. If deemed initially eligible, potential participant will be provided with instructions (and appointments, if applicable) for a physical exam, laboratory assessments, an electrocardiogram (ECG), and 1-minute rhythm strip. Some or all of these assessments may be at outside facilities.

Medical Assessments
The physical exam must be performed by a qualified physician and lab assessments must be completed at a designated lab. Medical assessments will include:

- Blood pressure, pulse, and body temperature measurement.
- Height and weight, which will be used to calculate Body Mass Index (BMI).
- Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen, and extremities.
- Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes, and cerebellar function).
- ECG and 1-minute rhythm strip.
- Clinical laboratory assessments, per Section 12.0 Clinical Laboratory Assessments. The clinical laboratory values will not be captured in the eCRF but will be used to establish eligibility and will be kept with the participant's source record. Clinically significant abnormal values will be captured as medical history.
- If there is evidence of liver disease by history, physical examination or laboratory testing, HCV serology will be performed.
- If there is evidence of significant hepatic disease other than HCV, the potential participant will not be eligible for enrollment and will be advised to see their personal physician for further evaluation. If HCV serology is positive and the potential participant has not already been evaluated for possible treatment of HCV, they will be referred to a physician with expertise in evaluating and treating liver disease. After this evaluation and after completion of any recommended treatment, if the HCV is judged by this physician to be relatively stable and of mild severity, the participant may be enrolled, if there are no other contraindications.
- If the potential participant has well-controlled hypertension 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 nuclear exercise testing by a cardiologist 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. Participants taking one or more antihypertensives may be enrolled in the study. The investigators will record and review medications used to control hypertension prior to enrollment. Per the Medical Monitor and site physician's instruction, other tests of

cardiovascular health and function may be required during screening, such as an echocardiogram. These will only be completed on a case-by-case basis to confirm a participant's cardiovascular eligibility.

Additional visits (in person, by telephone, or via telemedicine) 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.

Once all results are obtained, the site team will review all medical assessments, notes from interviews and discussions, medical records, and measures against eligibility criteria. If, upon examination, there are questions raised about possible medical problems, the site physician will request additional tests, assessments, or measures as indicated. The site physician may also contact outside providers with participant permission as needed. If deemed initially eligible, the site staff will schedule the IR screening and send results of LEC-5 and SCID-5-SPQ to the IR.

The study team will provide the participant with a location to complete the telemedicine visits at the study site. They will also provide technical support before the assessment and therapeutic support after, if needed. These assessments may be completed remotely with prior permission from the Medical Monitor and Independent Rater if it is deemed safe based on the participant's medical history and current presentation. For all IR visits, participants should have adequate internet access and be in a private and quiet space where they are comfortable talking about personal matters.

7.1.2 Independent Rater Screening Assessments

If participants meet initial eligibility during Screening, a blinded IR will continue the eligibility assessment via telemedicine after reviewing the results of the LEC-5 and SCID-5-SPQ. The blinded IR interview may be recorded to assess reliability of ratings. The potential participant should be present at the study site during this assessment unless the study team has received permission for the participant to complete the assessment remotely. In either case, the therapy pair will be available for support. If a participant reports suicidal ideation during this assessment, the IR will contact the therapy pair after the call and present any concerns. The therapy pair is then required to 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 to assess personality disorders. Only appropriate modules will be completed.
- 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 to assess psychiatric disorders.

The results from the MINI, SCID-5-PD, DDIS, and C-SSRS will be provided to the therapy pair 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,but the measures will not be repeated.

If the results of any interview indicate an exclusionary psychological disorder diagnosis is present, the Senior IR reviewer will review the recording of the MINI and/or SCID-5-PD assessment. The Senior IR reviewer will invite the study team (including therapists, site physician, and Clinical Investigator) to provide any additional information that may inform the Senior IR reviewer's opinion. The Senior IR reviewer will make the final judgment on whether or not the participant has an exclusionary diagnosis. Participants with exclusionary diagnoses

will not be enrolled. However, if any diagnosis is not present or uncertain according to any measure orinterview, but the investigator believes the participant presents with a particular disorder, they may diagnose and deem the participant ineligible if appropriate.

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

7.1.3 Enrollment

In advance of Visit 0, the site team will review all notes from Screening visits, medical assessments, IR assessments, notes, discussions, medical records, and measures against eligibility criteria. The Sponsor will additionally perform eligibility review prior to enrollment at the site. If the participant is eligible, medication tapering and concomitant medications dose adjustments will be discussed, if applicable. The site physician will consult the prescribing physician to initiate medication tapering for participants. For all details on concomitant medications, tapering, allowed, and prohibited medications refer to Section 11.0 Concomitant Medications.

At study onset, if a potential participant is eligible, the study team will contact the Medical Monitor and send a summary of the medical history for approval to enroll the potential participant. If a participant is determined to be eligible to participate in the study, the participant will be notified of enrollment at Visit 0. A medication tapering plan will be discussed with the participant, if applicable. Medical history and medication information will be reviewed for completeness. If agreeable, the participant will be enrolled in the study. Once enrolled, AE collection requirements begin (refer to Section 10.0 Safety). Visit 0 should take place within 2 to 14 days after Independent Rater Screening is completed. Visit 0 and Visit 1 may take place on the same day.

For eligible participants at Enrollment (Visit 0), qualified site staff will:

- Administer the MAPS-Adapted C-SSRS (Since Last Visit).
- Support participants in the completion of the following pre-treatment measures.
    - DRRI-II
    - ACE
    - OSU-TBI
    - UFEC
- Remind the participants of lifestyle modifications, including fasting and refraining from using psychoactive or non-approved medications, pertinent prior to the Experimental Session per Section 3.3 Lifestyle Modifications.

7.2 Preparatory Period with Enrollment Confirmation

7.2.1 Preparatory Sessions

Participants will undergo three Preparatory Sessions (Visits 1, 2, and 4) lasting approximately 90 minutes with the therapy pair prior to the first Experimental Session. The Preparatory Period will be initiated within 12 days of Visit 0. There must be at least 48 hours between Preparatory Sessions 1 (Visit 1) and 2 (Visit 2) and 72 hours between the Baseline CAPS-5-T1 (Visit 3) and Preparatory Session 3 (Visit 4). The minimum time to complete the Preparatory Period is 7 days. Adherence criteria for Preparatory Sessions should be followed per the Treatment Manual. In these visits the therapy pair 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.

Preparatory Sessions during the Preparatory Period will focus on psychoeducation about PTSD, building safety for the therapeutic relationship, developing the therapeutic alliance, obtaining the background for the trauma, and preparing the participant for the first Experimental Session.

- Preparatory Session 1 (Visit 1) will occur 0 to 12 days after Visit 0.
- Preparatory Session 2 (Visit 2) will occur at least 2 days after Visit 1 (depending on medication tapering).
- Preparatory Session 3 (Visit 4) will occur 3 to 6 days after the Baseline CAPS-5 (V3).

At each 90-minute psychoeducation and therapy Preparatory Session, the therapy pair will:

- Record the therapy session.
- Inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements. Record Aes as described in Section 10.0 Safety.
- Inquire about concomitant medication use and adherence.
- Discuss goals and expectations for the Experimental Session, following standard procedures and techniques described in the Treatment Manual [111].

If a participant would like a companion present during or after the Experimental Session, a meeting between the therapy pair and that individual will be scheduled prior to the first Experimental Session. There must be mutual agreement between the participant and therapy pair concerning the presence of the companion.

At any time during the Preparatory Period, if a potential participant is deemed to be ineligible, the site team will classify them as a Pre-randomization Early Termination, notify the potential participant that they are not eligible for the study, and not schedule additional assessments. The site team will not randomize participants classified as Pre-randomization Early Terminations.

During one of the Preparatory Sessions, if possible, the therapy pair will introduce the participant to the attendant who will remain with the participant during each overnight stay after each MDMA-assisted therapy session. The attendant will be an individual with previous training in caregiving. The site will make all attempts to have the same attendant for each Experimental Session for a given participant, but it is not guaranteed.

7.2.2 Baseline CAPS-5 by Independent Rater

At Baseline, an IR will measure the Baseline CAPS-5 (referred to as Baseline CAPS-5 T1) via telemedicine. This visit may be recorded to video to establish inter-rater reliability. The scores will be sent within 72 hours to the site staff. A CAPS-5 Total Severity Score of at least 28 is required to meet Enrollment Confirmation criteria. The IR will also administer the DSP-I and the SDS.

7.2.3 Baseline Self-Reported Measures

Qualified site staff will administer the MAPS-Adapted C-SSRS (Since Last Visit) and actively support participants in the completion of the following self-reported measures. These measures should be completed after the Baseline CAPS-5 and before the Treatment Period begins.

- WHOQOL-BREF
- AAQ-II

- SCS
- BPAQ-SF
- PCL-5
- MIES
- BDI-II
- CPGS
- PTGI

7.2.4 Enrollment Confirmation

The Preparatory Period ends with Enrollment Confirmation. A participant's enrollment will be confirmed if they have completed medication tapering, have a confirmed PTSD diagnosis per the CAPS-5 assessment with a Total Severity Score of 28 or greater, a total PCL-5 score of 36 or greater at Screening, continue to agree to all lifestyle modifications, and continue to meet all eligibility criteria.

7.3 Treatment Period

7.3.1 Experimental Sessions

There will be two or three Experimental Sessions, depending on group (Visits 5 and 9 for 2-session group; Visits 5, 9, and 13 for 3-session group). Procedures for MDMA-assisted therapy will remain the same across all sessions and all procedures regardless of assigned group. Experimental Sessions must be at least 6 to 8 hours long, measured from 30 minutes prior to IMP administration.

- Experimental Session 1 (Visit 5) will occur within 7 days after Preparatory Session 3 (Visit 4). If the Baseline CAPS-5 assessment is completed outside of the allowed window, the investigator should consult the CRA and Medical Monitor to determine if the assessment should be repeated. The first Experimental Session will include an initial dose of 120 mg of MDMA followed by a supplemental dose of 40 mg 1.5 to 2 hours after the initial dose unless tolerability issues emerge with the first dose or it is refused by the participant.
- Experimental Session 2 (Visit 9) will occur 21 to 35 days after Experimental Session 1 (Visit 5). An initial dose of 120 mg MDMA will be administered. A supplemental dose of 40 mg will be administered 1.5 to 2 hours after the initial dose unless tolerability issues emerge with the first dose or it is refused by the participant.
- Group 1 only: Experimental Session 3 (Visit 13) will occur 21 to 35 days after the second Experimental Session (Visit 9). An initial dose of 120 mg will be administered. A supplemental dose of 40 mg will be administered 1.5 to 2 hours after the initial dose unless tolerability issues emerge with the first dose or it is refused by the participant.

Table 9: Schedule of Procedures for Experimental Sessions

Approximate Time	Procedure or Action
8:30	Urine drug screen and pregnancy test, concomitant medicationinformation collected, self-reported measures and C-SSRS administered, participant acclimated to environment
8:55	Baseline BP, body temperature, pulse
9:00	**IMP Administration**, Begin video recording
10:30	BP, body temperature pulse **Supplemental Dose Administration**, unless tolerability issues emergewith the first dose or it is refused by the participant
16:30	C-SSRS, BP, body temperature, pulse

Pre-IMP Administration

- 24 to 48 hours prior to the first Experimental Session, the participant will be randomized.
- On the day of the Experimental Session, the participant will arrive approximately 30 to 60 minutes prior to IMP administration.
- The therapy pair will direct the participant to complete the PCL-5 and BDI-II and will administer the C-SSRS.
- The site team will ensure the participant has not used caffeine or nicotine 2 hours prior and has fasted for 10 hours prior to IMP administration and complied with all other requirements per Section 3.3 Lifestyle Modifications.
- 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 10.0 Safety.
- The site team will instruct the participant that they will not be able to use caffeine or nicotine at least 6 hours after the IMP administration.
- The site team will complete urine drug screen, pregnancy test, 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 pair 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.
- If the participant continues to be eligible, the session will proceed.
- Baseline blood pressure, body temperature, and pulse will be measured just prior to administration of the initial dose.

During the Experimental Session

- After video recording has begun, at approximately 9:00 in the morning, a qualified staff member will administer the initial dose of IMP with an electrolyte-containing fluid. 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 pair, who will provide guidance and support, as needed.
- After the first hour, if the participant has not spoken spontaneously, the therapy pair will check in with them about the nature of the experience. For the rest of the experience, as appropriate, the therapy pair will support and encourage the participant in emotional

processing and resolution of whatever psychological material is emerging, as described in the Treatment Manual.

- Water or Electrolyte-containing 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.
- If the participant prefers not to have the supplemental dose, the therapy pair will document the reason.
- The site physician will be contacted with a brief description of how the session is progressing and the recent vital signs. The site physician will approve or deny the administration of the supplemental dose. If an AE requiring medical attention has occurred between the initial and supplemental dose, the site physician will determine whether the supplemental dose is recommended or not. 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 electrolyte-containing fluid approximately 1.5 to 2 hours after the initial dose, unless tolerability issues emerge with the first dose or it is refused by the participant.
- Food will be provided during the latter part of the session.
- If there is an approved companion, that person may arrive as agreed upon but will wait in the waiting room until a member of the therapy pair brings them to the session room. Alternatively, the companion may arrive after the session has ended.

End of Experimental Session

- The therapy pair will record Aes and concomitant medications.
- Blood pressure, body temperature, and pulse will be measured approximately 8 hours after the initial dose.
- The therapy pair will administer the C-SSRS.
- The session may be ended if all medical and psychiatric parameters are acceptable, elevations in vital signs have resolved to pre-IMP levels, the participant is alert, ambulatory, and emotionally stable, and the night attendant has arrived.
- The therapy pair or site physician shall remain available to participants via 24-hour cellular phone for support, as needed.

Overnight Stay

- The participant will remain overnight with the therapy pair or a night attendant in accordance with site SOPs.
- Participants will remain overnight in an appropriately furnished room at or near the study site until after the Integrative Session the morning after each Experimental Session. With prior approval of the therapy pair, a companion may accompany the participant during the overnight stay.
- An attendant will check in periodically on the participant during the overnight stay, even if a companion is present. The attendant will monitor participant condition and will help participants relax during the overnight stay. The attendant will be an individual with some previous training in caregiving and will be supportive but not intrusive. If there is an emergency or the participant needs additional support, the attendant can contact the therapy pair.
- The participant and a companion (if applicable) will receive information that will allow them to contact the therapy pair during the overnight stay in the case of an emergency or to request additional support.
- Participants will be encouraged to use much of the time during their overnight stay for rest and as a period of reflection and integration in a quiet atmosphere.

- Participants may not drive until after the Integrative Session and cleared by therapist, as emotional processing may impair their attention and focus.

7.3.2 Telephone Contact After Experimental Sessions

The goal of the telephone contact is to assess health changes, ensure participant safety, and offer support. A member of the therapy pair will follow-up with the participant by telephone on every other day for 14 days after each Experimental Session (starting 2 days post-Experimental session) Each call will last on average five 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 pair or participant.

At each telephone contact, the member of the therapy pair 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 10.0 Safety.
- Inquire about concomitant medication use and adherence.
- Offer support in accordance with the Treatment Manual.
- Administer the Since Last Visit C-SSRS.

7.3.3 Integrative Sessions

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

Treatment 1

- Integrative Session 1.1 (Visit 6): morning after Experimental Session 1 (Visit 5).
- Integrative Session 1.2 (Visit 7): ~1 week (3 to 14 days) after Experimental Session 1 (Visit 5).
- Integrative Session 1.3 (Visit 8): ~2 weeks (10 to 21 days) after Experimental Session 1 (Visit 5). This visit serves two purposes: to continue integration and to prepare for the next Experimental Session.

Treatment 2

- Integrative Session 2.1 (Visit 10): morning after Experimental Session 2 (Visit 9).
- Integrative Session 2.2 (Visit 11): ~1 week (3 to 14 days) after Experimental Session 2 (Visit 9).
- Integrative Session 2.3 (Visit 12): ~2 weeks (10 to 21 days) after Experimental Session 2 (Visit 9) This visit serves two purposes: to continue integration and to prepare participants in Group 1 (3-Session Group) for the next Experimental Session.

Treatment 3 (3-Session Group only)

- Integrative Session 3.1 (Visit 14): morning after Experimental Session 3 (Visit 13)
- Integrative Session 3.2 (Visit 15): ~1 week (3 to 14 days) after Experimental Session 3 (Visit 13).
- Integrative Session 3.3 (Visit 16): ~2 weeks (10 to 21 days) after Experimental Session 3 (Visit 13). This visit will be the final Integrative Session prior to entering the Post-Treatment Period.

During Integrative Sessions, the therapy pair will:

- Record the session.

- Inquire about any possible changes in health. Assess the participant's mental health and the status of any previously recorded AEs. Record AEs as described in Section 10.0 Safety.
- Inquire about concomitant medication use and adherence.
- Discuss and review events that occurred with the participant during the Experimental Session, including thoughts, feelings, and memories. If necessary, the therapy pair will help the participant to reduce any residual psychological distress they are experiencing. The therapy pairs 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 pairs will be supportive, validate the experience, and facilitate understanding and emotional clearing.
- Be accessible for additional support via phone or telemedicine if needed.

7.4 Post-treatment Period and Study Termination

7.4.1 Post-treatment Period

After the last Integrative Session, participants will enter follow-up for approximately 4 weeks with no protocol required visits until the Outcome CAPS-5 T2 assessment. This assessment will also include the SDS and the DSP-I. Participants will have access to therapy pairs for support if needed, and additional visits via phone, telemedicine, or in person can be scheduled if requested. Participants will continue to comply with protocol requirements for concomitant medications until after Study Termination.

Participants will be scheduled for an in-person visit within 1 to 7 days after the CAPS-5 T2, where qualified site staff will arrange the post-treatment blood draw, administer the MAPS-Adapted C-SSRS (Since Last Visit), and actively support participants in the completion of the self-reported outcome measures.

- WHOQOL-BREF
- AAQ-II
- SCS
- BPAQ-SF
- PCL-5
- MIES
- BDI-II
- CPGS
- PTGI
- UFEC
- AUDIT
- DUDIT

Participants in the two Experimental Session group will have a second outcome evaluation (T2.2, Visit 15) timed to be concurrent with those who completed three Experimental Sessions, approximately 4 weeks after their first post-treatment assessment at T2 (Visit 13). A blinded IR from the IR Pool will conduct the assessments via telemedicine. These assessments may be recorded to establish inter-rater reliability. Participants will be instructed to withhold from sharing with the IRs their progress in the study including how many visits or Experimental Sessions they have had.

Participants who have withdrawn from treatment will also complete a final CAPS-5 assessment immediately upon withdrawal. The IR will also administer the DSP-I and the SDS.

Following post treatment assessment, participants will engage in post treatment planning with the treatment team and are no longer required to comply with requirements related to concomitant medication or other forms of therapy.

7.4.2 Study Termination

Study Termination will take place 1 to 7 days after the final CAPS-5 assessment. Participants who have withdrawn from treatment but have continued for follow-up will also complete this assessment immediately upon withdrawal.

The site team will:

- Inquire about any possible changes in health. Assess the participant's mental health and the status of any previously recorded AEs. Record AEs as described in Section 10.0 Safety.
- Inquire about concomitant medication use and adherence.
- Measure weight (used to calculate BMI).
- Measure blood pressure.
- Administer the MAPS-Adapted C-SSRS (Since Last Visit).
- Support the participant in the completion of the PCL-5 and BDI-II (2-Session Group only).
- Provide and discuss a Post-Study Plan.
- Actively support participant in completion of Study Termination self-reported measures.

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 Post-Study Plan, which may include a referral for additional medical or therapeutic care, as described in Section 7.4.3 Post-Study Plan.

7.4.3 Post-Study Plan

At Study Termination, participants will be provided with a Post-Study Plan. 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 Post-Study Plan at their last contact. Screen Failures will be provided a referral if requested.

8.0 Investigational Medicinal Product

8.1 Description of Active Compounds

The Active Pharmaceutical Ingredient (API) to be used in this protocol is MDMA (as hydrochloride salt). This ring-substituted phenethylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and re-uptake inhibitor. Its direct actions on serotonergic, adrenergic, and other receptors are considerably lower. Refer to the IB for a comprehensive review of the pharmacology effects and proposed mechanisms of action of the investigational Medicinal Product (IMP). Mannitol and magnesium stearate serve as inactive excipients. All capsules are HPMC. MDMA HCl is referred to throughout as MDMA.

8.1.1 Doses

This study will compare the effects of two versus three manualized Experimental Sessions of therapy assisted by divided doses of MDMA. Initial doses per Experimental Session include 120 mg MDMA HCl, followed 1.5 to 2 hours later by a supplemental dose (40 mg MDMA HCl). Total amounts of MDMA HCl to be administered per Experimental Session range from 120 to 160 mg. Refer to Table 2: Dose Regimen of MDMA.

8.1.2 Stability

IMP was manufactured and packaged according to Good Manufacturing Practices (GMP). Stability studies for the IMP are ongoing. All required Chemistry Manufacturing and Control (CMC) submissions will be made to the IND.

8.2 Handling

8.2.1 Encapsulation, Packaging, and Labeling

Each package will be an open-label container that will be used as bulk presentation at the study site. Each dose of MDMA can be dispensed by the Schedule I license holder or designee. Additional doses of MDMA that are not administered to a participant will be kept in the open-label container for administration in future sessions or to other participants.

All labels will comply with local, state, and federal regulations. Each Package will be labeled with a protocol number, IMP name, lot number, sponsor name and contact information. A statement that the IMP is restricted to clinical trial use only will be included on each package. All labels will comply with US regulations.

8.2.2 Accountability

Forms will be provided to track IMP accountability and administration throughout the study. Open-label IMP accountability and administration logs will be reviewed by the sponsor. MDMA will be accounted for per capsule dispensed, based on the doses to be administered at each Experimental Session for any given participant. IMP will be handled in accordance with all local, state, and federal regulations and forms pertaining to the use of Schedule I controlled substances, and forms will be maintained by the appropriate controlled substance license holder or delegate.

8.2.3 Storage

MDMA is a controlled substance and will be stored securely and handled in compliance with all relevant federal, state and local regulations. In accordance with these requirements, the appropriate license holder or designee will be responsible for storing, dispensing, and administering the MDMA.

8.2.4 Administration

IMP will be administered orally at the study site. All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each Experimental Session. Supplemental doses should be administered unless withheld or declined. Each dose (initial and supplemental) will be administered with a glass of water.

A person at the site authorized to manage and administer controlled substances will dispense the appropriate number of capsules for each Experimental Session.

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant federal, state, and local regulations.

8.2.5 Treatment Compliance

Compliance to protocol required doses will be guaranteed by the person licensed to manage and administer controlled substances for Experimental Sessions at each site. All administered doses will be recorded for IMP accountability. The IMP will be stored securely per regulations.

8.3 Randomization and Participant Numbering

Every potential participant who is prescreened by telephone according to the IRB-approved script will be assigned a Screening Number by the site. This Screening Number should be recorded on the Screening Log.

Each participant who passes pre-screening and is scheduled to complete Screening assessments will be assigned a ten-digit alphanumeric Participant Number. Eligible participants will be enrolled in the study and sequentially assigned an identification number. One character of this Participant Number will be updated for participants who reach Enrollment Confirmation at Visit 4. Please see the MPVA6 Study Operations Manual for taxonomy details. All participants will also be assigned a unique participant identifier within the database for use in analysis.

Participants will be randomized in 1:1 allocation to two versus three sessions of MDMA-assisted therapy.

8.4 Blinding and Bias Minimization

Eligibility will be determined by review of screening by the PI, site team and Sponsor Medical Monitor prior to enrollment.

To further minimize bias in measuring effectiveness, the sponsor will use an observer-blind, centralized, reliable IR pool to administer the Primary Outcome measure via live video interviews. The IR Pool will have no knowledge of AEs and will only evaluate participants at Baseline and at the assessments scheduled after each Experimental Session. The IR Pool is blinded to full study design, visit number, treatment assignment, number of treatments, and any data from the treating therapy pair after Baseline. IRs will be assigned to participants based on availability. Participants will be instructed to withhold study progress from IRs. Timing of CAPS-5 assessments are pre-specified in the study protocol within visit windows.

To ensure that all participants regardless of group assignment are treated in a similar manner, the sites 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 to 8 hours long. Adherence to the Treatment Manual will be randomly checked by review of video by blinded 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 randomized participants who receive at least one dose of IMP and complete at least one follow-up assessment will be included in the final mITT set.

The Safety Review Committee will act in an advisory capacity to the site to monitor participant safety, data quality, and review outcomes to ensure the trial is conducted safely, ethically, and meets endpoint objectives.

9.0 Risks

9.1 Non-drug Related Risks

9.1.1 Medical Assessments

In preparation for MDMA-assisted therapy sessions, blood draws and a full medical examination, including a physical examination, ECG, 1-minute rhythm strip, and laboratory tests, are required to establish eligibility for the study. 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. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

9.1.2 PTSD, Suicide Risk, and Therapy

During Screening, throughout MDMA-assisted therapy, and during assessment of study measures, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses or suicidal ideation as a result of recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress and exacerbate suicidal ideation during and immediately after therapy sessions. Therapy is conducted as part of this study, and people undergoing therapy are expected to confront unpleasant thoughts, feelings, and memories in the process. Because therapy is an integral part of the research study design, the potential distress arising from therapy is unavoidable. Therapy pairs will provide emotional support to participants during any psychological distress.

The therapy pair will minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with a history of suicide attempts will not be excluded unless significant risk of suicidal behavior is present at the time of Screening. Participants will be enrolled according to the Eligibility Criteria based on the clinical judgment of the site physician, therapy pair, and Medical Monitor.

A qualified individual will administer the C-SSRS according to the Time and Events-Study Measures Table, and as needed depending on clinical presentation of the participants, to monitor for development and intensity of suicidal ideation and/or behavior. The therapy pair will implement the following plan to assess elevated or imminent suicide risk.

If the C-SSRS or other clinical information reveals current serious Suicidal Ideation (scores of four or greater), indicating risk at the time of the assessment, or positive Suicidal Behavior (scores of one or greater), the participant will be referred for further management as described below.

1. If the participant has current suicidal ideation, but no specific plan to commit suicide (Suicidal Ideation Score=4), the individual administering the C-SSRS will ensure:
    a. The participant is evaluated by the investigator and/or site physician to determine an appropriate course of action. Findings will be discussed with the participant and their personal therapist, if applicable.

b. Regular check-ins via phone or in-person will be continued until the participant has stabilized or a new course of action is taken based on changes in C-SSRS score and/or ongoing clinical assessment.
c. Notification of the sponsor within 24 hours of this event and provide a narrative for the AE for expedited reporting to FDA. Increases in suicidality will be captured as an AESI per Section 10.1.1 Adverse Events of Special Interest and evaluated for seriousness. SAEs will be reported per regulatory guidance.
d. Treatment would be continued when deemed appropriate by the investigator and Medical Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up.

2. If the participant has suicidal ideation, and a plan to commit suicide (Suicidal Ideation Score=5) or positive Suicidal Behavior (Score greater than or equal to 1), the individual administering the C-SSRS will assess whether the risk is imminent. A Suicidal Ideation score of five does not necessarily indicate an immediate risk if the thoughts are fleeting, fairly easily controlled, and deterrents are strong. If there is no imminent risk, the individual will follow the procedure described above. If there is imminent risk of suicidal behavior, the individual will ensure:
    a. Participants are evaluated by the investigator or site physician to determine an appropriate course of action, and the therapy pair will contact their personal therapist, who will be invited to come to the study site to assist, depending on their location.
    b. If it is determined that the participant is at imminent risk of suicide, the therapy pair will do one of the following:
        i. If on site with the participant, escort them to the ED;
        ii. If not on site with the participant (e.g., telephone or telehealth appointment), call EMS and ensure that the participant is transferred to the responding medical personnel.
    c. If the participant will not comply and wishes to leave without consultation, call VA police if on site. Explain that the participant is in immediate danger of committing suicide. Provide a complete description of the participant and give any other needed details to ensure the participant's safety.
    d. Notification of appropriate members of the study team and sponsor representatives within 24 hours, provide a narrative for the AE for expedited reporting to FDA.
    e. The event will be collected as an AESI per Section 10.1.1 Adverse Events of Special Interest and seriousness will be evaluated. SAEs will be reported per regulatory guidance. Treatment would be continued when deemed appropriate by the investigator and Medical Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up.

9.1.3 Recorded Content

All therapy sessions and IR assessments may be recorded for research and training purposes. Participants may feel uncomfortable with having their sessions recorded. The recordings are necessary for developing the experimental treatment and assessing adherence to the Treatment Manual. Any requests for use of video outside of research and training requests will result in participants receiving information on the request. They will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

The sponsor uses encrypted, secure technology to transfer and store recordings, but there is always a risk of a security breach. The sponsor is committed to taking preventative measures to avoid such an event. In the case of a security breach, the participant will be notified, and all efforts will be made to minimize the dissemination of recorded content.

9.2 Risks of Receiving MDMA

Study procedures and eligibility criteria have been developed based on Phase 2 and Phase 3 PTSD clinical trials which exclude potential participants with pre-existing exclusionary medical conditions that would exacerbate risk. The therapy pairs and site physicians are available via telephone throughout the study if any problem occurs when a participant is not at the site. In the event of a medical emergency or any other medical problem during an Experimental Session, the site physician should be immediately available by telephone, and based on assessment of the situation, they should make the decision to either evaluate the participant themselves at the site or arrange for transfer of the participant to the Emergency Department.

Further information on the risks associated with MDMA can be found in the IB and risk mitigation procedures are described by risk category below. Risk Categories were determined by review of possible risks within the Risk Assessment and Categorization Tool (RACT).

9.2.1 High Level Risks

High Risk does not indicate an event is more likely to happen but indicates per the RACT assessment that new and or more complex procedures are required in the study to ensure screening is adequate to eliminate or manage the risk in the patient population. No high-level risks have been identified in this study.

9.2.2 Medium Level Risks

Medium Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that new or many procedures, which are not complex, are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

9.2.2.1 Cardiovascular and Cerebrovascular Risks and Mitigation

MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes should last no more than 8 hours. Participants with PTSD in MAPS-sponsored Phase 2 and Phase 3 studies do not appear to differ from healthy individuals in this sympathomimetic, physiological response. 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 blood

pressure and to a lesser extent diastolic blood pressure. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.

Risks posed by elevated blood pressure are addressed by excluding people with pre-existing uncontrolled hypertension and monitoring blood pressure and pulse, as described in Section 3.2 Exclusion Criteria. Before and after IMP administration in Experimental Sessions, the therapy teams monitor vital signs. The therapy teams should attend to clinical signs and symptoms of potential rare complications of the cardiovascular effects of MDMA, such as stroke or acute myocardial infarction (AMI). during Experimental Sessions. Any symptoms such as chest pain, shortness of breath, neurological deficit or confusion or other potential indicators of end organ effects should prompt additional vital sign measurements, and intervention if appropriate. Therapy teams should notify the site physician if this occurs for evaluation.

If any participant has neurological deficits, as assessed by the site physician, whether or not they are associated with hypertensive crisis, they should be monitored (as described above) and a rapid response team should be called if medically indicated. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be sufficient time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [112].

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, the study physician will be contacted immediately, and a rapid response team will be called to assess the patient and act in accordance with the assessment of the expert on site supported by national and local/AHA and European Society of Cardiology (ESC) Guidelines. Pending transport to the hospital the site team may take any measures ordered by the site physician including administering medication such as aspirin or nitroglycerin or providing supplemental oxygen per local standards. If further evaluation at the hospital reveals that the participant has had an AMI, they will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in participants who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [113]. Any participant who experiences such medical complications during an Experimental Session will not be given another Experimental Session, and will be followed up for safety.

QT interval will be evaluated in the event of hospitalization for management of cardiovascular or cerebrovascular event. If at any time a participant develops a QT/QTc interval > 450 ms or of >30 ms over Baseline during ECG evaluation, the participant should be discontinued from treatment.

9.2.2.2 Psychological Risks and Mitigation

MDMA may expose or exacerbate any underlying psychological distress, which could arise from the onset of MDMA effects until the last effects have dissipated, or even later. 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. In clinical studies, these symptoms have been self-limiting and have responded well to reassurance from the therapy pair, with occasional use of benzodiazepines for anxiety. In this study, participants will have the intention of confronting and working through traumatic experiences.
Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute reactions. The potential for destabilizing psychological distress will be minimized by:

- Excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder type 1 or with psychotic disorders)
- Preparatory Sessions of non-drug therapy before the Experimental Session
- Creating an atmosphere of trust during the Experimental Session
- Close monitoring
- Phone contact with participants during the week after the Experimental Session
- Integrative Sessions
- Overnight stays at the study site for the night of each Experimental Session. Qualified personnel will be available during the overnight stay to respond to the needs of the participant. Attendants will be instructed to contact the therapy pair upon request or at the appearance of signs of a potential SAE.

During the Preparatory Sessions, participants should be made aware of the fact that difficult emotions, including grief, rage, fear, or panic, may arise during Experimental Sessions. Every effort should be made to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the Experimental Session, including empathic listening on the part of the therapy pair and performance of diaphragmatic breathing by participants.

If the participant is severely agitated, anxious, in danger of self-harm or suicide, or is experiencing any other severe psychological distress, at the end of a therapy session, at least one member of the therapy pair will remain with the participant for at least 2 more hours. During this time, the therapy pair will employ affect management techniques, will talk with the participant to help them gain cognitive perspective of their experiences, and will help the participant implement the self-soothing and stress inoculation techniques presented during the Preparatory Sessions. If the participant remains severely anxious, agitated, in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of the 2-hour stabilization period, the site physician and therapy pair will decide between the following options:

1. If severe distress occurs at the end of an Experimental Session, a nurse, therapeutic assistant, physician, or therapy pair member should stay with the participant until the severe distress resolves or until the time of their Integrative Session appointment the following morning. The therapy pair should then meet with the participant daily until the period of destabilization has passed.
2. If the participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an Experimental Session, a site physician may prescribe a benzodiazepine (specifically, lorazepam) and/or sleep aid (e.g., zolpidem). The route, frequency, and dose should be determined by the site physician. If these medications are stocked on site, they should be stored according to applicable national and local regulations. This medication will be captured on the Concomitant Medications eCRF. The site physician should not prescribe an SSRI, SNRI, or monoamine oxidase inhibitor (MAOI) in this context, unless it has been determined that the participant will be withdrawn from the study. Residual symptoms will be addressed during the frequent follow-up therapy visits with the therapy pair.
3. If a participant should become psychotic, arrangements should be made to stabilize them or transfer them to the Emergency Department if hospitalization is necessary. Any participant who is hospitalized after a severe psychological reaction will be suspended

from the protocol until after recovery or stabilization, at which time the investigator and/or site physician will carefully evaluate the participant's emotional status.

For those participants engaged in an ongoing therapeutic relationship with a therapist or psychiatrist, the participant's outside therapist(s) should be involved in the management of any psychiatric complications. For those participants engaged in an ongoing therapeutic relationship with the investigator or member of the therapy pair, the management of any psychiatric complications should be undertaken by them in their capacity as the participant's therapist.

9.2.3 Low Level Risks

Low Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no new or complex procedures are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

9.2.3.1 Thermoregulatory Risks and Mitigation

MDMA administered in a controlled setting produces only a slight increase in body temperature [114]. Ambient temperature does not enhance or attenuate this slight elevation in humans. In data gathered from sponsor-supported Phase 2 and Phase 3 studies, it was found that compared to placebo, a higher percentage of participants receiving MDMA had peak body temperatures greater than 1 degree Celsius (° C) above Baseline. However, there was no strong relationship between dose of MDMA and peak body temperature or between MDMA dose and elevation above threshold of 1° C above Baseline.

Ambient temperature should be kept at a comfortable level during Experimental Sessions. 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 at any time the temperature rises more than 1.5° C above Baseline despite these efforts, the site physician should be consulted for further evaluation and treatment.

9.2.3.2 Osmoregulatory Risk and Mitigation

MDMA administered in a controlled setting is not expected to have any risks of osmoregulatory changes. Participants are not allowed to drink more than three liters of water over the course of the Experimental Session and fluid intake will be spread out appropriately during the session. If a participant exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an Experimental Session, they should not receive another Experimental Session unless it is approved by the investigator, site physician, and the Medical Monitor.

9.2.3.3 Genotoxicity Risk and Mitigation

The standard genotoxicity battery for MDMA has demonstrated that MDMA is negative for in vitro and in vivo genotoxicity, both with and without metabolic activation.

9.2.3.4 Reproductive and Developmental Risks and Mitigation

There are no data from the use of MDMA in pregnant women. In the absence of these data, epidemiological studies of Ecstasy are the only source of human data. One of two studies of Ecstasy users suggests that use of Ecstasy and polydrug use during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [115, 116].

Studies in rats and rabbits have not shown direct or indirect harmful effects with respect to reproductive toxicity. Repeated dose toxicity studies of adequate duration, fertility, early embryonic development, and embryofetal development studies of MDMA with toxicokinetics have been completed. These studies established the "no-observed-adverse-effect level" (NOAEL) dose to be excluded the highest dose level evaluated at ≤10 mg/kg/day (supratherapeutic dose) in both sexes of the rat for fertility, reproductive performance, and for maternal and developmental toxicity in the rabbit. The NOAEL dose was the highest dose level evaluated at ≤15 mg/kg/day (supratherapeutic dose) for maternal and developmental toxicity in the rat. Due to the short half-life and single-dose dosing regimen of MDMA, pre- and post-natal development studies are not considered necessary for assessment of risk to the unborn. Assessment of embryofetal risk based on all available non- clinical and clinical data supports unlikely human teratogenicity/fetotoxicity in early pregnancy. On the basis of male fertility studies, the embryofetal risk posed from treatment of male participants with MDMA is also unlikely.

People who are able to become pregnant are included in the studies in this program, defined as those who are fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Postmenopausal state is defined as no menses for 12 months without an alternative medical cause. As a precautionary measure in clinical trials, participants who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session, which are conducted in monthly intervals, and must agree to use adequate contraception at least for the duration of the study during the Treatment Period which is 10 days post the last dose of MDMA. The end of relevant systemic exposure to MDMA is approximately 48 hours [117].

9.2.4 Minimal Risks

Minimum Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no procedures are needed beyond basic monitoring to ensure screening is adequate to eliminate or manage the risk in the patient population.

9.2.4.1 Common Expected AEs

Common expected AEs were typically observed during Experimental Sessions, but were transient and typically diminished as the MDMA was metabolized and excreted over the next 72 hours after dosing. In the Phase 3 study MAPP1, the most common adverse events reported more frequently reported in the MDMA group were muscle tightness, decreased appetite, dizziness, nausea, hyperhidrosis, feeling cold, restlessness, mydriasis, dizziness (postural), bruxism, nystagmus, increased blood pressure, feeling jittery, chest pain (non-cardiac), dry mouth, vision blurred, pollakiuria, intrusive thoughts, vomiting, stress, and musculoskeletal chest pain. AEs were typically self-limiting.

9.2.4.2 Neurotoxicity Risk

It does not appear that MDMA-assisted therapy negatively impacts cognitive function based on data from Phase 2 studies sponsored by MAPS. The sponsor has carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies.

9.2.4.3 Abuse Potential

Despite its classification as a Schedule I drug, an examination of findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants, such as cocaine or methamphetamine. There have been no AESIs reported in Phase 2 and Phase 3 studies that could be suggestive of abuse potential among research study participants treated with MDMA. Diversion is not an issue for sponsor-supported studies because MDMA is only administered under the supervision of the clinical investigator and no take-home doses are permitted. MDMA administration and handling follows all regulations pertaining to the use of controlled substances within research studies.

Studies assessing prevalence of problematic Ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop problematic Ecstasy use or dependence. An observational long-term follow-up assessment conducted at least 12 months after participation in a MAPS-sponsored early Phase 2 PTSD study of MDMA-assisted therapy found that 8.7% (8 of 92) participants reported using Ecstasy subsequent to study participation, with 6 of these 8 participants having used Ecstasy prior to study enrollment. Several participants volunteered that they would not seek out MDMA outside of a psychotherapeutic setting.

10.0 Safety

10.1 Adverse Events

In accordance with guidance for the specific study site, FDA Safety Reporting Requirements for INDs and BA/BE Studies, an Adverse Event (AE) is defined as any medical occurrence in a participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

Events related to planned treatments or physician visits for Baseline conditions collected in the medical history will not be collected, unless there is an exacerbation of the condition, in which case they will be actively followed until resolution.

An unexpected AE is one that is not listed in the current IB or an event that is by nature more specific or more severe than a listed event.

The site physician will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The therapy pairs will collect AEs during study visits from Enrollment (Visit 0) through Study Termination. Participants will be asked directly how they are feeling during each contact, and AEs may be captured spontaneously during therapy sessions, telephone calls, or other correspondence. Completed measures may create suspicion that an AE occurred; in this case, the site staff should follow-up with the participant.

All AEs will be monitored by the therapy pair until resolution or, if the AE becomes chronic, a cause can be identified. If an AE is unresolved when a participant terminates from the study, a clinical assessment will be made by the site physician, investigator, and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" eCRF will be determined by the site physician as:

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

The seriousness and 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.

10.1.1 Adverse Events of Special Interest

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.

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.

The subset of AEs involving suicide risk under the following terms are also of special interest:

- Suicides
- Suicide attempts
- 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 AEs will be marked in the eCRF with the denotation "Adverse Event of Special Interest" (AESIs) whether serious or non-serious.

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" (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 via the eCRF within 24 hours of the site's awareness of the event.

10.1.2 Serious Adverse Events

In accordance with 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, an SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the event causes substantial disruption of a person's ability to conduct normal life functions).
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent permanent impairment or damage.
- Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

AEs which do not fall into these categories are defined as non-serious. It should be noted that a severe Adverse Event need not be serious in nature and that a SAE need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as a study-related SAE, unless, in the view of the site physician, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the participant was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis, or elective abortion does not result in an SAE report, unless, in the view of the site physician, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

All SAEs will be collected from the time of informed consent through Study Termination. All SAEs which occur during the course of the trial, whether considered to be associated with IMP or not, must be reported to the sponsor within 24 hours of the site staff's awareness of occurrence. Reporting procedures will be provided to the site. All SAEs will be assessed for relationship, expectedness and any required actions to address safety at the time of reporting of the event. SAEs will be evaluated by the site physician and Medical Monitor to determine if it is appropriate for the participant to continue treatment or enter follow-up. Any participant who experiences a SAE considered related to the IMP administration will be permanently discontinued from future IMP treatments

10.2 Other Significant Events

Significant life events that may occur during the course of the study, including death of a loved one, loss of employment, or other hardship, may have an impact on treatment outcome. The sponsor will capture these life events using the LEC-5 measure. Such events will be entered as Comments in the eCRF and if appropriate, described in the Case Study Report for data outliers, if any.

10.3 Pregnancy

10.3.1 Definition of 'Able to Become Pregnant'

A participant is considered able to become pregnant if they were assigned female at birth and are post-menarche. A participant is considered not able to become pregnant if they are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), postmenopausal, or assigned male at birth.

10.3.2 Contraception Guidelines

Study participants who were assigned male at birth with partners who are able to become pregnant will not be required to practice contraception. Adequate contraception is required for all participants of who are able to become pregnant, regardless of sexual activity, sexual orientation, or the sex of their partner. Abstinence from penile-vaginal intercourse is not an adequate contraception plan by itself; participants must agree to a back-up method (e.g., condoms with spermicide) if they do choose to engage in penile-vaginal intercourse. It is recommended to stock condoms with spermicide at the study site to provide to participants if they need them. Adequate contraception methods include:

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Non-oral hormonal methods, including injected, intravaginal, implanted, transdermal
- Oral hormones plus a barrier contraception (condom, diaphragm, or spermicide)
- Double barrier method (at least two of the following: condom, diaphragm, and spermicide)
- Vasectomized sole partner

For questions about acceptable contraception methods, contact the Medical Monitor.

10.3.3 Follow-up Requirements

Details of all pregnancies in study participants will be collected after Enrollment (Visit 0) and collected through 10 days after the last Experimental Session. Pregnancies should be reported to the sponsor via telephone or email within 24 hours of site staff awareness.

In the event of a pregnancy, the participant will discontinue Experimental Sessions but may continue with non-drug Integrative Sessions, the next CAPS-5 assessment, and Study Termination procedures. At a minimum, prior to withdrawal from the study, efforts should be made to assess the final CAPS-5 immediately and complete Study Termination procedures. The participant will be emergency unblinded if the participant wishes as described in Section 8.4 Blinding and Bias Minimization, after the final CAPS-5 assessment.

The investigator will collect follow-up information on the participant and neonate and forward to the sponsor until the outcome of the pregnancy, which will be reported on an optional Pregnancy eCRF. Any termination, elective or spontaneous, will be reported. Abnormal pregnancy outcomes, such as spontaneous abortion, fetal death, stillbirth, congenital abnormalities, or ectopic pregnancy, will be reported as SAEs.

10.4 Medical Monitor

The name and contact information for the Medical Monitor is:

Kelly Green, PA-C, MPH
Associate Medical Director, MAPS Public Benefit Corporation
Email: kelly.green@mapsbcorp.com
Phone number: 877-748-3767

Medical Monitor contact information will also be provided in a separate contact list.

11.0 Concomitant Medications

11.1 Tapering Instructions

The site physician will record concomitant medications during Screening. If the prospective participant is being treated with psychiatric medications at enrollment, the prospective participant will be encouraged to discuss medication tapering with their outside treating physician, if any, and will be required to give the site physician permission to do so as well. Additionally, participants who are taking prohibited opiates will be cross-tapered to an allowable opiate (hydrocodone, morphine, and codeine) under the care of their prescribing physician.

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 11.2 Allowed Concomitant Medications). The prescribing physician's opinion about medication discontinuation will be documented either in writing from the prescribing physician, or in writing by the site physician documenting phone contact with the prescribing physician. Tapering will follow a time course appropriate for the medication based on its half-life, with the Baseline CAPS-5 T1 (Visit 3) scheduled to occur after complete washout for psychological medications and Experimental Session 1 (Visit 5) scheduled to occur after complete washout for medications with drug-drug interactions without a psychological concern (five half-lives plus at least 1 week for stabilization).

The therapy pair 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 also inquire about concomitant medication adherence and document all information on the Concomitant Medications eCRF.

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

11.2 Allowed Concomitant Medications

The site physician may prescribe necessary and appropriate medications in accordance with local and state regulations during the study to treat AEs that do not respond to other management outlined in the Treatment Manual. Examples include concomitant benzodiazepines for uncontrolled anxiety (for example, lorazepam at modest doses and occasional use only to avoid withdrawal effects of discontinuation between Experimental Sessions) or sleep aids (excluding trazodone) in compliance with Section 11.3 Prohibited Medications.

Gabapentin or certain opiates will be allowed when prescribed for pain management. The following opiates will be allowed during the study: hydrocodone, morphine, and codeine. Prior to randomization, participants who are taking opiates not included on this list will be cross-tapered to an allowable opiate under the care of their prescribing physician. Opiate medications may reduce the efficacy of MDMA and may prolong QT/QTc interval, but the opiates that are allowed during this trial have been selected because they have the lowest potential for QT/QTc interval prolongation. Individuals using opiates for pain management will be asked to decrease the dose leading up to the Experimental Session in order to avoid withdrawal effects when they are required to refrain from taking the medication from 12 hours before IMP administration at the Experimental Session to 24 hours after. During this period, the participant will be allowed to take the medication if needed for intolerable pain flare-ups or to prevent withdrawal symptoms. If a participant reports lack of analgesic effect during the sub-acute period following each Experimental Session, the site physician may approve taking an allowed opiate medication sooner than 24 hours after IMP administration.

If the participant is on stimulants for Attention Deficit/Hyperactivity Disorder (ADHD) at Baseline, they can continue to use them at the same dose and frequency, as long as they discontinue five half-lives before each Experimental Session and do not restart for 10 days after each Experimental Session.

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

11.3 Prohibited Medications

To be enrolled in the study, participants must:

- Refrain from the use of any psychoactive medication not approved by the research team from Baseline through Study Termination (with the exception of gabapentin or certain opiates for pain control).
- 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.
- Agree that, for 1 week preceding each Experimental Session they will refrain from:
    - Taking any specified herbal supplement (except with prior approval of the research team).
- Agree that, for 5 half-lives of the medication preceding each Experimental Session they will refrain from:

- Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen) 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).

Use of Marijuana, St. John's Wort, and other herbs and medicines with notable serotonergic effects are prohibited from Baseline to Study Termination. Any investigational treatments under study for PTSD treatment are prohibited from use concurrent with this study.

Diphenhydramine is excluded from this study unless prior approval is granted by the site physician.

If an SSRI, SNRI, MAOI, or other antidepressant is used between Experimental Session 1 (Visit 5) and Study Termination, the participant will be withdrawn from treatment and continue in follow-up.

Opiates other than hydrocodone, morphine, and codeine are prohibited from Enrollment Confirmation to Study Termination. Participants taking prohibited opiates will be cross-tapered to an allowable opiate during the Preparatory Period. Participants whose Experimental Sessions are delayed by the COVID-19 pandemic may start any of these medications during the delay, as clinically indicated. When study visits resume, they will be given the option to resume Experimental Sessions after tapering off of these medications, per the tapering plan described above.

12.0 Clinical Laboratory Assessments

The site physician will confirm laboratory assessments gathered in screening for assessing eligibility. The site physician will use a 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 following laboratory assessments will be performed as a part of Screening:

- Serum electrolytes and metabolic profile
  - Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT)
  - Albumin:globulin (A:G) ratio
  - Albumin, serum
  - Alkaline phosphatase, serum
  - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT)
  - Bilirubin, total
  - Blood urea nitrogen (BUN):creatinine ratio
  - Calcium, serum
  - Carbon dioxide
  - Chloride, serum
  - Creatinine, serum
  - Globulin, total
  - Glucose, serum
  - Potassium, serum
  - Protein, total, serum
  - Sodium, serum

- CBC
    - Hematocrit
    - Hemoglobin
    - Mean corpuscular volume (MCV)
    - Mean corpuscular hemoglobin (MCH)
    - Mean corpuscular hemoglobin concentration (MCHC)
    - Red cell distribution width (RDW)
    - Percentage and absolute differential counts
    - Red blood cell (RBC) count
    - White blood cell (WBC) count
- Urinalysis
    - Color
    - Appearance
    - Specific gravity
    - pH
    - Protein
    - Glucose
    - Ketones
    - Occult blood
    - Leukocyte esterase
    - Nitrite
    - Bilirubin
    - Urobilinogen
- Thyroid function
    - Thyroid-stimulating hormone (TSH) high sensitivity (if abnormal, free T3 and T4 will also be tested)
- HCV if indicated
- %Carbohydrate deficient transferrin (%CDT) to detect heavy alcohol use
- Urine-dip pregnancy test for participants who are able to become pregnant will be performed at the site
- Urinary drug test will be performed at the site

Laboratory assessments, with the exception of urine pregnancy and drug tests, will be performed at the nearest clinical laboratory to the 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).

13.0 Statistical Considerations

Key personnel, MAPS, and the biostatistician will agree on a Statistical Analysis Plan prior to database lock, which will provide more detail about analyses than provided in this protocol. An overview of the statistical analyses that will be performed is provided in the following sections.

13.1 Power and Sample Size Determination

In this equivalence design the primary hypothesis is a comparison of 3 sessions of MDMA with therapy versus 2 sessions of MDMA with therapy. The internal validity of this study is predicated upon data already established and approved by the FDA showing that 3 sessions of MDMA with therapy has proven superiority over placebo in the treatment of PTSD. Therefore, it is appropriate to compare the effectiveness of the experimental arm of 2 sessions of MDMA to the effectiveness of the previously established 3 doses in order to test an equivalence hypothesis. If the null hypothesis is rejected, the alternative hypothesis will be accepted which states that 2 sessions of

MDMA shows equivalent efficacy as 3 sessions. The measure of effectiveness is the change from baseline in the CAPS-5 Total Severity Score. In this equivalency design the "zone" of equivalence is a pre-defined region above or below the difference in mean changes in the CAPS-5 Total Severity Score in the arm given 3 sessions of MDMA. In a previous study, MP16, it was reported that the mean change in baseline among 29 participants with PTSD who were given 3 sessions of MDMA experienced a mean reduction of 30.7 in the CAPS-5 Total Severity Score, with a standard deviation of 12.7. Therefore, the "zone" of equivalence in this study is defined as a mean change in the CAPS-5 Total Severity Score in the arm given 2 sessions of MDMA that is within 11 points of the mean change in that seen in the arm given 3 sessions. If similar results are observed as those seen from the sponsor's 3 session MP16 study, we would conclude equivalence if the difference in mean changes in CAPS-5 Total Severity Score in the arm given 2 sessions of MDMA was as low as -19.7 to as high as -41.7. Assuming that in the population of PTSD patients there is no difference in the mean change in CAPS-5 Total Severity Score when given 2 sessions of MDMA or 3 sessions of MDMA, with alpha level set at 5%, power set to 90%, the sample size of this study is 30 participants per arm.

13.2 Statistical Analyses

Descriptive statistics will be computed overall, as well as by MDMA-assisted session condition, for all available data from outcome measures, time course of onset of treatment effect and including minimum, maximum, average, median, and standard deviation.

The following analysis sets are defined for this study:

- All Enrolled: all participants who sign informed consent and are initially enrolled
- mITT: all randomized participants who receive Investigational Product in at least one Experimental Session and have at least one follow-up CAPS-5 assessment
- Per Protocol (PP): all randomized participants who receive Investigational Product in assigned number of Experimental Sessions (depending on randomization group) and have completed post-treatment CAPS-5 assessments
- Not Per Protocol (NPP): all participants who are included in the mITT Set but not the PP Set
- Safety: all participants who receive any IMP

13.2.1 Primary Effectiveness Analysis

The groups will be compared from T1 (Baseline) to T2 (Primary Outcome Visit) using post-treatment mean change in symptom severity, as assessed by the mean change in CAPS-5 Total Severity Score. The mean change from baseline to T2 (Primary Outcome Visit) will be summarized by treatment group along with confidence intervals. If the primary null hypothesis is rejected, mean change in SDS score from Baseline to T2 (Primary Outcome Visit) will be analyzed. In a previous study, MAPP1, it was reported that the standard deviation of the mean change in baseline among 37 participants with PTSD who were given 3 sessions of MDMA 11.5. Recalculations of the equivalence zone with 90% power provide the "zone" of equivalence for the difference in means in this study will be [-10, 10].

The null hypothesis is formulated as:

$$\text{Ho: } (\mu 1 - \mu 2) \leq -10 \text{ or } (\mu 1 - \mu 2) \geq 10$$

The alternative hypothesis is formulated as:

H_1: $-10 < (\mu 1 - \mu 2) < 10$

The null hypothesis will be tested using the two-one-sided-test (TOST [reference added at end]) procedure. The 90% confidence interval around the difference of the means will be compared to the interval of equivalence. If both of the bounds are inside the equivalence interval, we will reject the null hypothesis and conclude the effect of 3 sessions of MDMA with therapy is equivalent to the effect of 2 sessions. If the primary effectiveness hypothesis is rejected, the secondary effectiveness hypothesis will be tested.

13.2.2 Secondary Effectiveness Analysis

The SDS will be analyzed in a similar manner to the primary analysis of the CAPS-5 using an equivalence zone of [-2.25, 2.25].

13.2.3 Exploratory Analyses

An exploratory responder analysis will further characterize clinical significance of PTSD treatment effect in the mITT set after each Experimental Session 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 11 or less and no longer meeting PTSD diagnostic criteria on CAPS-5
- The primary effectiveness analysis will be performed in the same method above using the CAPS-5 measure from visit T2.2 in the 2 Session treatment group compared to the T2 Session in the 3 Session treatment group.

Exploratory analyses may be conducted, when possible, to evaluate effectiveness by assigned treatment group, actual exposure, and the impact of 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, and number of Experimental Sessions completed) on treatment effect. Further details of the exploratory analyses of secondary outcome measures will be provided in the Statistical Analysis Plan.

13.2.4 Safety Analyses

Safety analyses will confirm safety data with summary tables listing exposure to IMP, unsolicited AEs, concomitant medications, suicidal ideation and behavior, and vital signs overall and by group. If a participant has more than one AE mapped to the same PT, that AE will be reported once using the highest severity. AEs that occur on Day 0 (Experimental Session), Day 1, Day 2 after IMP administration will be presented separately. Assess relative incidence of AEs during Experimental Sessions such as clinical signs and symptoms, such as chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that may be indicative of a medical complication of the IMP.

Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized by treatment group, analysis set, and category. Concomitant medications taken on Day 0 (Experimental Session), Day 1, Day 2 after IMP administration will

be presented separately. Any psychiatric concomitant medications will be tabulated by period (Preparatory, Treatment Period, Follow-up Period). Frequency and incidence of positive or serious ideation and suicidal behavior will be presented using descriptive statistics of C-SSRS scores in tabular format. Vital signs (heart rate, blood pressure, and body temperature) for Experimental Sessions will be summarized using descriptive statistics in tabular format listing values at pre-IMP administration, prior to the supplemental dose, and at the end of each Experimental Session by treatment group. Additional details are available in the Statistical Analysis Plan.

13.2.5 Interim Analysis

An interim analysis may be performed before all participants in the mITT set have completed the final CAPS-5 assessment and terminated treatment, including early termination participants who have completed their final CAPS-5. The objective of the interim analysis is to assess whether the sponsor wants to add additional subjects to the study. Additional details and statistical methodology for the sample size re-estimation will be provided in the Statistical Analysis Plan.

13.2.6 Safety Review Committee

The sponsor will appoint a Safety Review Committee with appropriate expertise in the conduct of clinical trials to monitor subject safety information during this study, conduct the interim analysis, and make associated recommendations for all reviews. The Safety Review Committee is an advisory group commissioned and charged with the responsibility of periodically evaluating cumulative safety and other clinical trial data for evidence of safety concern and recommending study continuation, discontinuation, or modification. The composition of the Safety Review Committee will include clinician experts, MAPS PBC senior management and biostatistician. The Safety Review Committee will periodically review safety reports and data on safety outcome measures, to assess suitability of continuation of the study.

14.0 Study Governance

The sponsor, MAPS, holds the IND for MDMA and is responsible for funding the Clinical Development Program. The sponsor has delegated the primary responsibility of trial organization to MAPS PBC, including designing, initiating, managing, coordinating, continuing, and concluding the clinical trials within the Clinical Development Program. MAPS PBC is tasked with maintaining the quality of study conduct through ongoing monitoring of data and participating in writing study publications. MAPS PBC contracts with independent entities who represent clinical sites to accomplish these goals. Collectively, MAPS and MAPS PBC are referred to as sponsor throughout this document.

14.1 Ethics

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), with applicable local regulations.

The protocol and the ICF must be reviewed and approved by a properly constituted institutional review board (IRB) or ethics committee and national regulatory agency (FDA) before study start. Signed and dated documentation of approvals must be provided to the sponsor. Prior to study start, the investigator is required to sign a signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor.

14.1.1 Financial Disclosure

Investigators will adequately and accurately disclose financial interests to the sponsor prior to study start, during the study if financial interests change, and 1 year after study completion. The sponsor will submit necessary disclosures to the appropriate regulatory bodies.

14.1.2 Informed Consent

The investigator and therapy pair are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the participant into the trial.

Potential participants may be sent the ICF to review after the initial phone screen. Preferably, informed consent will be obtained by the therapy pair that will treat the participant. Information about the study must be given orally and in an understandable written ICF. The informed consent discussion must be conducted by a person who is qualified according to federal, state, or local regulations. The participant should have the opportunity to inquire about details of the study and to consider participation.

The therapy pair may meet with the potential participant via telemedicine for ICF review and signing prior to in person screening if necessary for scheduling of screening activities. If this is completed by telemedicine visit, the pair will ensure the ICF is thoroughly explained and reviewed just as it would be at an in-person visit. If the potential participant is still interested after review, they will sign the consent during that telemedicine visit. Site staff (preferably the therapy pair who would be treating this potential participant) 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. The participant will then bring their signed copy of the ICF to their next in person visit where study staff will then counter sign the ICF, copy the ICF for the participant and file the original at the site. The signature may instead be obtained using an electronic 21 CFR Part 11 compliant system due to COVID- 19.

In addition to the explanation of study visits, the information should include that access to original medical records and processing of coded personal information must be authorized. A written release is needed to give permission to site staff to request and view the participant's medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

Eligible participants may only be included in the study after signing the IRB approved ICF. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol beyond phone screening). The process of obtaining informed consent should be documented in the participant's source records. The study staff will provide a copy of the signed ICF to the participant and will maintain the original in the ISF.

The written ICF and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised ICF and written information should receive approval from an IRB before use. The participant should be informed in a timely manner if new information becomes available that may affect the decision to take part or continue in the study. The communication of this information should be documented. Participants can withdraw consent at

any time without prejudice. If a participant withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the study team will have full access to their medical records, including termination visit information. If a participant revokes only the HIPAA authorization, the study team will have full access to all medical records prior to the date and time of revocation.

If a participant fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.

14.2 Study Monitoring, Auditing, and Documentation

Investigators, therapy pairs, and all study staff will be trained prior study start for each site. Study sites will be monitored by site visits and telephone calls by representatives of the sponsor. In addition, critical data and systemic issues will be subject to centralized monitoring via the EDC system to develop and evaluate strategies for correction across sites. Sites will be monitored as appropriate for the rate of enrollment to comply with GCP guidelines and to ensure validity of study data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on eCRFs, source records, and IMP accountability records. An eCRF collation will be completed for each participant enrolled within the EDC system.

Videos from selected sessions will be reviewed for adherence to the Treatment Manual as described in Section 5.4 Adherence to Therapeutic Method. Findings from video reviews may be discussed with therapy pairs as needed to ensure continued adherence to the protocol.

During or after the study, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, eCRFs, and other protocol documentation for on-site audit or inspection. Monitoring and auditing procedures will be supplied in a separate document.

14.2.1 Source Records

Source records contain all primary evidence of existence of the participant and document all study procedures. Source records include but are not limited to medical records, measures, checklists, notes, emails, and laboratory reports. All data reported in the eCRF are transcribed from primary source documents and must be consistent. These documents are maintained at the study site securely. Source records of CAPS-5 assessments will be stored in dedicated limited access files during the study.

14.3 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants. Despite this, privacy cannot be guaranteed. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data. If past medical records are needed, participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. In accordance with the guidance for a specific study site location, Clinical Trials (GUIDE-0068) or FDA E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), all assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators who are directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social

security number. Only personnel listed on the MPVA-6 Site Responsibilities Log and the MAPS PBC Sponsor Delegation Log can have access to documents containing Protected Health Information (PHI).

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. The sponsor will utilize confidentiality procedures to assure participant privacy. Audiovisual recordings are necessary for sponsor oversight of therapy processes. Any requests for use of audiovisual recordings outside of research and training requests will result in participants receiving information on the request. Participants will have control over any presentation of audiovisual recordings beyond viewing by authorized researchers, sponsor staff, or regulatory agencies. The sponsor uses encrypted, secure technology to transfer and store recordings, but there is always a risk of a security breach. The sponsor is committed to taking preventative measures to avoid such an event. In the case of a security breach, the participant will be notified, and all efforts will be made to minimize the dissemination of recorded content.

Clinical trial data other than audiovisual recordings will be hosted on an EDC system that is FDA-compliant. All data entered into this system will be de-identified. Participants will only be referred to by numbers and a secondary identifier code. Source Records and identifying information will be retained at clinical sites per GCP. The sponsor will train the study staff on EDC procedures. Each study staff member with access to the data will be given an individual password.

The sponsor has developed a feature that will allow participants to create a password and enter their self-report questionnaire data directly into Medrio using the electronic Participant Reported Outcome (ePRO) feature. Participants will be reminded by email to enter the data. Participant emails will be treated as Protected Health Information (PHI) in the database. Participants will receive a welcome email and reminder emails to ensure that they provide all necessary data.

14.4 Costs to Participants

There will be no costs to the study participants for participation. The sponsor will cover all direct costs of study procedures required for participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of a participant’s condition that are unrelated to the research study or any unrelated procedures will not be covered by the Sponsor. Participants who previously received therapy from a therapy pair member prior to the study, and who will continue to receive ongoing treatment outside of the study from that therapist, are responsible for those non-study related costs. Participants may be reimbursed for reasonable expenses incurred for study participation, such as local travel to the treatment site; this will be specified in each site’s consent.

14.5 Treatment and Compensation for Study Related Injury

Some study-related emergencies can be treated by the site physicians. If the site physicians cannot treat a study-related emergency, then there are contingency plans for the transport of participants to the nearest hospital. Treatment of a study-related emergency would first be billed to a participant’s health insurance provider. If the participant's private or employer health insurance plan does not cover clinical trial-related claims, then the sponsor will cover any treatment costs directly related to the study. The sponsor will not cover costs of ongoing treatment unrelated to the study due to pre-existing conditions, or the cost of the participant's time spent obtaining treatment for pre-existing conditions before receiving treatment in the study. In the event of a suit against the sponsor, the sponsor carries third-party insurance that will cover bodily injury claims and will pay for applicable legal defense if needed/warranted.

14.6 Record Retention

Investigators must retain all study records required by the sponsor and applicable ICH-GCP, FDA regulations in a secure and safe facility. The Investigator must consult a representative of the sponsor before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the ISF. It is the responsibility of the sponsor to inform the investigator or institution when these documents no longer need to be retained. Medical records will be maintained according to the James J Peters VA medical center’s requirements. Research Investigator files at JJP VAMC will be destroyed six years after the end of the fiscal year when the research project has been completed per Records Schedule DAA-0015-2015-0004-0032.

14.7 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. For multi-center studies, 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 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.

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.

References

1. Ot'alora, G.M., et al., *3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial.* J Psychopharmacol, 2018. **32**(12): p. 1295-1307.

2. Mithoefer, M.C., et al., *3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial.* Lancet Psychiatry, 2018. **5**(6): p. 486-497.

3. American Psychiatric Association, *The Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. 2013, Washington, DC: American Psychiatric Association.

4. Lanius, R.A., et al., *The dissociative subtype of posttraumatic stress disorder: rationale, clinical and neurobiological evidence, and implications.* Depress Anxiety, 2012. **29**(8): p. 701-8.

5. Lanius, R.A., et al., *Emotion modulation in PTSD: Clinical and neurobiological evidence for a dissociative subtype.* Am J Psychiatry, 2010. **167**(6): p. 640-7.

6. Nicholson, A.A., et al., *The Dissociative Subtype of Posttraumatic Stress Disorder: Unique Resting-State Functional Connectivity of Basolateral and Centromedial Amygdala Complexes.* Neuropsychopharmacology, 2015. **40**(10): p. 2317-26.

7. Hoge, C.W., et al., *Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care.* N Engl J Med, 2004. **351**(1): p. 13-22.

8. *Statement Of Jon A. Wooditch Acting Inspector General Department Of Veterans Affairs*, in *Committee On Veterans' Affairs Subcommittee On Disability Assistance And Memorial Affairs*. 2005: Washington, DC.

9. Solon, O., *My therapist gave me a pill: Can MDMA help cure trauma?* https://www.theguardian.com/society/2016/sep/16/mdma-ptsd-therapy-trauma-maps-medical-study#comments, in *The Guardian*. 2016.

10. US Department of Veterans Affairs, *Annual Benefits Report Veterans Benefits Administration Fiscal Year 2018.* 2018, VA Benefits Administration: Washington, DC.

11. Kemp, J. and R. Bossarte, *Suicide Data Report 2012*. 2013, US Department Of Veterans Affairs, Mental Health Services, Suicide Prevention Program http://www.va.gov/opa/docs/Suicide-Data-Report-2012-final.pdf%20.

12. Brady, K., et al., *Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial.* JAMA, 2000. **283**(14): p. 1837-44.

13. Davidson, J.R., et al., *Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder.* Arch Gen Psychiatry, 2001. **58**(5): p. 485-92.

14. Friedman, M.J., et al., *Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting.* J Clin Psychiatry, 2007. **68**(5): p. 711-20.

15. Arikian, S.R. and J.M. Gorman, *A Review of the Diagnosis, Pharmacologic Treatment, and Economic Aspects of Anxiety Disorders.* Prim Care Companion J Clin Psychiatry, 2001. **3**(3): p. 110-117.

16. Sidran Institute. *Post traumatic stress disorder fact sheet*. 2016; Available from: http://www.sidran.org/wp-content/uploads/2018/11/Post-Traumatic-Stress-Disorder-Fact-Sheet-.pdf
Accessed July 2021.

17. Ursano, R.J., et al., *Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder.* Am J Psychiatry, 2004. **161**(11 Suppl): p. 3-31.

18. Foa, E.B., et al., *Effective Treatments for PTSD, Practice Guidelines from the International Society for Traumatic Stress Studies*. Second ed. 2009, New York, NY: Guilford Press.

19. Benish, S.G., Z.E. Imel, and B.E. Wampold, *The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: a meta-analysis of direct comparisons.* Clin Psychol Rev, 2008. **28**(5): p. 746-58.

20. Cukor, J., et al., *Emerging treatments for PTSD.* Clin Psychol Rev, 2009. **29**(8): p. 715-26.

21. Basoglu, M., E. Salcioglu, and M. Livanou, *A randomized controlled study of single-session behavioural treatment of earthquake-related post-traumatic stress disorder using an earthquake simulator.* Psychol Med, 2007. **37**(2): p. 203-13.

22. Gerardi, M., et al., *Virtual reality exposure therapy using a virtual Iraq: case report.* J Trauma Stress, 2008. **21**(2): p. 209-13.

23. Heresco-Levy, U., et al., *Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder.* Int J Neuropsychopharmacol, 2002. **5**(4): p. 301-7.

24. Freudenmann, R.W., F. Oxler, and S. Bernschneider-Reif, *The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents.* Addiction, 2006. **101**(9): p. 1241-5.

25. Shulgin, A.T., *The background and chemistry of MDMA.* J Psychoactive Drugs, 1986. **18**(4): p. 291-304.

26. Farre, M., et al., *Pharmacological interaction between 3,4-methylenedioxymethamphetamine (ecstasy) and paroxetine: pharmacological effects and pharmacokinetics.* J Pharmacol Exp Ther, 2007. **323**(3): p. 954-62.

27. Liechti, M.E. and F.X. Vollenweider, *The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers.* J Psychopharmacol, 2000. **14**(3): p. 269-74.

28. Liechti, M.E. and F.X. Vollenweider, *Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies.* Hum Psychopharmacol, 2001. **16**(8): p. 589-598.

29. Tancer, M. and C.E. Johanson, *The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2007. **189**(4): p. 565-73.

30. Hysek, C.M., et al., *The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ("ecstasy") in humans.* Clin Pharmacol Ther, 2011. **90**(2): p. 246-55.

31. Hysek, C.M., et al., *Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone or in combination.* Int J Neuropsychopharmacol, 2014. **17**(3): p. 371-81.

32. Liechti, M.E. and F.X. Vollenweider, *Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans.* Eur Neuropsychopharmacol, 2000. **10**(4): p. 289-95.

33. Huizink, A.C., et al., *Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study.* Bmj, 2006. **332**(7545): p. 825-8.

34. Lieb, R., et al., *Mental disorders in ecstasy users: a prospective-longitudinal investigation.* Drug Alcohol Depend, 2002. **68**(2): p. 195-207.

35. von Sydow, K., et al., *Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults-a transient phenomenon? Results from a longitudinal community study.* Drug Alcohol Depend, 2002. **66**(2): p. 147-59.

36. Foa, E.B., *Prolonged exposure therapy for PTSD: emotional processing of traumatic experiences: therapist guide*. 2007, New York: Oxford University Press.

37. Wilbarger, P. and J. Wilbarger, *Sensory defensiveness and related social/emotional and neurological problems*. 1997, Van Nuys, CA.: Avanti Education Program.

38. Siegel, D.J., *The Developing Mind*. 1999, New York: Guilford Press.

39. Ogden, P., K. Minton, and C. Pain, *Trauma and the body: A sensorimotor approach to Psychotherapy*. New York. 2006, W. W. Norton and Company.

40. Bedi, G., et al., *Effects of MDMA on sociability and neural response to social threat and social reward.* Psychopharmacology (Berl), 2009. **207**(1): p. 73-83.

41. Gamma, A., et al., *3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans.* Neuropsychopharmacology, 2000. **23**(4): p. 388-95.

42. Rasmusson, A.M. and D.S. Charney, *Animal models of relevance to PTSD.* Ann N Y Acad Sci, 1997. **821**: p. 332-51.

43. Davis, M. and C. Shi, *The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety?* Ann N Y Acad Sci, 1999. **877**: p. 281-91.

44. Phelps, E.A., et al., *Activation of the left amygdala to a cognitive representation of fear.* Nat Neurosci, 2001. **4**(4): p. 437-41.

45. Metzner, R. and S. Adamson, *Using MDMA in healing, psychotherapy and spiritual practice*, in *Ecstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA.*, J. Holland, Editor. 2001, Inner Traditions: Rochester VT. p. 182-207.

46. Stolaroff, M., *The Secret Chief Revealed: Conversations with a pioneer of the underground therapy movement*. 2004, Sarasota FL: Multidisciplinary Association for Psychedelic Studies.

47. Mithoefer, M.C., et al., *The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study.* J Psychopharmacol, 2011. **25**(4): p. 439-52.

48. Bouso, J.C., et al., *MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder.* J Psychoactive Drugs, 2008. **40**(3): p. 225-36.

49. Greer, G.R. and R. Tolbert, *A method of conducting therapeutic sessions with MDMA.* J Psychoactive Drugs, 1998. **30**(4): p. 371-379.

50. Shulgin, A.T. and D.E. Nichols, *Characterization of three new psychotomimetics*, in *The Pharmacology of Hallucinogens*, R.C. Stillman and R.E. Willette, Editors. 1978, Pergamon: New York.

51. Anderson, G.M.d., et al., *Absolute configuration and psychotomimetic activity.* NIDA Res Monogr, 1978. **22**: p. 8-15.

52. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects.* J Clin Psychopharmacol, 2000. **20**(4): p. 455-66.

53. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2002. **162**(4): p. 396-405.

54. Tancer, M. and C.E. Johanson, *Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP.* Drug Alcohol Depend, 2003. **72**(1): p. 33-44.

55. Vollenweider, F.X., et al., *Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers.* Neuropsychopharmacology, 1998. **19**(4): p. 241-51.

56. Grinspoon, L. and J.B. Bakalar, *Can drugs be used to enhance the psychotherapeutic process?* Am J Psychother, 1986. **40**(3): p. 393-404.

57. Adamson, S., *Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances*. 1985, San Francisco CA: Four Trees Publications.

58. Shulgin, A. and A. Shulgin, *Pihkal: A Chemical Love Story*. 1st ed. 1991, Berkeley, CA: Transform Press. 1-978.

59. Downing, J., *The psychological and physiological effects of MDMA on normal volunteers.* J Psychoactive Drugs, 1986. **18**(4): p. 335-40.

60. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting.* Journal of psychoactive drugs, 1986. **18**(4): p. 319-327.

61. Grob, C.S., et al., *Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations.* Behav Brain Res, 1996. **73**(1-2): p. 103-7.

62. Grob, C., *MDMA research: preliminary investigations with human subjects.* Int J Drug Policy, 1998. **9**(2): p. 119-124.

63. Mithoefer, M.C., et al., *Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study.* J Psychopharmacol, 2013. **27**(1): p. 28-39.

64. Oehen, P., et al., *A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD).* J Psychopharmacol, 2013. **27**(1): p. 40-52.

65. Chabrol, H. and P. Oehen, *MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder.* J Psychopharmacol, 2013. **27**(9): p. 865-6.

66. Mithoefer, M.C., et al., *MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials.* Psychopharmacology (Berl), 2019. **236**(9): p. 2735-2745.

67. Feduccia, A.A., et al., *Breakthrough for trauma treatment: Safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline.* Frontiers in Psychiatry, 2019. **10**: p. 1-7.

68. Jerome, L., et al., *Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials.* Psychopharmacology (Berl), 2020. **237**(8): p. 2485-2497.

69. Mitchell, J.M., et al., *MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study.* Nat Med, 2021. **27**(6): p. 1025-1033.

70. Weathers, F.W., et al., *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. 2013, National Center for PTSD: Interview available at www.ptsd.va.gov.

71. Sheehan, D., *The Anxiety Disease*. 1983, New York, NY: Scribner's.

72. Leon, A.C., et al., *Assessing psychiatric impairment in primary care with the Sheehan Disability Scale.* Int J Psychiatry Med, 1997. **27**(2): p. 93-105.

73. Posner, K., et al., *Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants.* Am J Psychiatry, 2007. **164**(7): p. 1035-43.

74. Posner, K., et al., *The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults.* Am J Psychiatry, 2011. **168**(12): p. 1266-77.

75. Sheehan, D.V., et al., *The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.* J Clin Psychiatry, 1998. **59 Suppl 20**: p. 22-33;quiz 34-57.

76. Lecrubier, Y., et al., *The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI.* Eur Psychiatry, 1997. **12**(5).

77. Sheehan, D.V., et al., *The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability.* Eur Psychiatry, 1997. **12**(5): p. 232-241.

78. First, M.B., et al., *User's Guide for the SCID-5-PD (Structured Clinical Interview for DSM-5 Personality Disorder)*. SCID 5. 2015, Arlington, VA: American Psychiatric Association.

79. Weathers, F.W., et al., eds. *The Life Events Checklist for DSM-5 (LEC-5). Instrument obtainable from National Center for PTSD www.ptsd.va.gov*. 2013, National Center for PTSD: www.ptsd.va.gov.

80. Weathers, F.W.L.B.T., et al. *The PTSD Checklist for DSM-5 (PCL-5). Available at www.ptsd.va.gov*. 2013.

81. Ross, C.A., et al., *Differentiating Multiple Personality Disorder and Dissociative Disorder Not Otherwise Specified.* Dissociation, 1992. **5**(2): p. 87-90.

82. Eidhof, M.B., et al., *Dissociative Subtype of PTSD Interview (DSP-I) FOR DSM-5*. 2017, self-published by authors.

83. Steuwe, C., R.A. Lanius, and P.A. Frewen, *Evidence for a dissociative subtype of PTSD by latent profile and confirmatory factor analyses in a civilian sample.* Depress Anxiety, 2012. **29**(8): p. 689-700.

84. Wolf, E.J., et al., *The dissociative subtype of PTSD: a replication and extension.* Depress Anxiety, 2012. **29**(8): p. 679-88.

85. Wolf, E.J., et al., *A latent class analysis of dissociation and posttraumatic stress disorder: evidence for a dissociative subtype.* Arch Gen Psychiatry, 2012. **69**(7): p. 698-705.

86. Felitti, V.J., et al., *Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study.* Am J Prev Med, 1998. **14**(4): p. 245-58.

87. Anda, R.F., et al., *Childhood Abuse, Household Dysfunction, and Indicators of Impaired Adult Worker Performance.* Perm J, 2004. **8**(1): p. 30-8.

88. Dong, M., et al., *Insights into causal pathways for ischemic heart disease: adverse childhood experiences study.* Circulation, 2004. **110**(13): p. 1761-6.

89. Dube, S.R., et al., *The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900.* Prev Med, 2003. **37**(3): p. 268-77.

90. McBeth, J., et al., *Associations between adverse events in childhood and chronic widespread pain in adulthood: are they explained by differential recall?* J Rheumatol, 2001. **28**(10): p. 2305-9.

91. Beck, A.T., et al., *An inventory for measuring depression.* Arch Gen Psychiatry, 1961. **4**: p. 561-71.

92. Beck, A.T. and R.A. Steer, *Internal consistencies of the original and revised Beck Depression Inventory.* J Clin Psychol, 1984. **40**(6): p. 1365-7.

93. Beck, A.T., et al., *Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients.* J Pers Assess, 1996. **67**(3): p. 588-97.

94. Storch, E.A., J.W. Roberti, and D.A. Roth, *Factor structure, concurrent validity, and internal consistency of the Beck Depression Inventory-Second Edition in a sample of college students.* Depress Anxiety, 2004. **19**(3): p. 187-9.

95. Dixon, D., B. Pollard, and M. Johnston, *What does the chronic pain grade questionnaire measure?* Pain, 2007. **130**(3): p. 249-53.

96. Smith, B.H., et al., *The Chronic Pain Grade questionnaire: validation and reliability in postal research.* Pain, 1997. **71**(2): p. 141-7.

97. Neff, K., *The Development and validation of a scale to measure self-compassion.* Self and Identity, 2003. **2**: p. 223-250.

98. Neff, K.D. and R. Vonk, *Self-compassion versus global self-esteem: two different ways of relating to oneself.* J Pers, 2009. **77**(1): p. 23-50.

99. Saunders, J.B., et al., *Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II.* Addiction, 1993. **88**(6): p. 791-804.

100. Allen, J.P., et al., *A review of research on the Alcohol Use Disorders Identification Test (AUDIT).* Alcohol Clin Exp Res, 1997. **21**(4): p. 613-9.

101. Berman, A.H., et al., *Evaluation of the Drug Use Disorders Identification Test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample.* Eur Addict Res, 2005. **11**(1): p. 22-31.

102. Nash, W.P., et al., *Psychometric evaluation of the Moral Injury Events Scale.* Mil Med, 2013. **178**(6): p. 646-52.

103. Tedeschi, R.G. and L.G. Calhoun, *The Posttraumatic Growth Inventory: measuring the positive legacy of trauma.* J Trauma Stress, 1996. **9**(3): p. 455-71.

104. Tedeschi, R.G. and L.G. Calhoun, *Expert comparisons; Posttraumatic growth in clinical practice*, in *Handbook of posttraumatic growth: Research and practice*, L.G. Calhoun and R.G. Tedeschi, Editors. 2006, Erlbaum: Mahwah, NJ. p. 291-310.

105. Bryant, F.B. and B.D. Smith, *Refining the architecture of aggression: A measurement model for the Buss–Perry Aggression Questionnaire.* J Research in Personality, 2001. **35**(2): p. 138-167.

106. Bond, F.W., et al., *Preliminary psychometric properties of the Acceptance and Action Questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance.* Behav Ther, 2011. **42**(4): p. 676-88.

107. *Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group.* Psychol Med, 1998. **28**(3): p. 551-8.

108. Skevington, S.M., et al., *The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group.* Qual Life Res, 2004. **13**(2): p. 299-310.

109. Vogt, D., et al., *Deployment risk and resilience inventory-2 (DRRI-2): an updated tool for assessing psychosocial risk and resilience factors among service members and veterans.* J Trauma Stress, 2013. **26**(6): p. 710-7.

110. Corrigan, J.D. and J. Bogner, *Initial reliability and validity of the Ohio State University TBI Identification Method.* J Head Trauma Rehabil, 2007. **22**(6): p. 318-29.

111. Mithoefer, M., *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder; Version 8.1*. 2017: http://www.maps.org/research/mdma/mdma-research-timeline/4887-a-manual-for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd.

112. Powers, W.J., et al., *Guidelines for the early management of patients With acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2019. **50**(12): p. e344-e418.

113. Ryan, T.J., et al., *1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction).* J Am Coll Cardiol, 1999. **34**(3): p. 890-911.

114. Liechti, M.E., A. Gamma, and F.X. Vollenweider, *Gender differences in the subjective effects of MDMA.* Psychopharmacology (Berl), 2001. **154**(2): p. 161-8.

115. McElhatton, P.R., et al., *Congenital anomalies after prenatal ecstasy exposure [letter].* Lancet, 1999. **354**(9188): p. 1441-2.

116. Bateman, D.N., et al., *A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England.* Eur J Clin Pharmacol, 2004. **60**(9): p. 635-41.

117. Mueller, M., et al., *Direct comparison of (+/-) 3,4-methylenedioxymethamphetamine ("ecstasy") disposition and metabolism in squirrel monkeys and humans.* Ther Drug Monit, 2009. **31**(3): p. 367-73.