Protocol and Synopsis MAPPUSX
IND #063384

A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Therapy for the Treatment of Participants with Posttraumatic Stress Disorder

CURRENT APPROVED PROTOCOL	Amendment 2, Version 1, 06 July 2021
AMENDED PROTOCOL	Amendment 3, Version 1, 15 March 2023
SPONSOR	Multidisciplinary Association for Psychedelic Studies (MAPS) 3141 Stevens Creek Blvd #40563 San Jose, CA 95117
SPONSOR REPRESENTATIVE	Rick Doblin, Ph.D. Executive Director MAPS
SPONSOR DELEGATE &TRIAL ORGANIZER	MAPS Public Benefit Corporation 3141 Stevens Creek Blvd #40547 San Jose, CA 95117
SPONSOR DESIGNEE	Amy Emerson Chief Executive Officer MAPS Public Benefit Corporation Email: amy@mapsbcorp.com
CLINICAL INVESTIGATOR	Multi-site Study
MEDICAL MONITOR	MAPS Public Benefit Corporation Phone number: +1 (877)-748-3767 Additional contact information is available in the Study Operations Manual
USE	In conjunction with relevant Food and Drug Administration (FDA), Health Canada (HC), and Israeli Ministry of Health (MOH) guidance

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
MAPPUSX Original Protocol, Version 1	27 July 2020
MAPPUSX Amendment 1, Version 1	19 January 2021
MAPPUSX Amendment 2, Version 1	06 July 2021

Amendment 3, Version 3: 15 March 2023

This amendment is considered to be substantial.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in the protocol amendment is to revise adverse event definitions and reporting, inclusion/exclusion criteria, and restructure the risk section to align with FDA guidance and the Investigator's Brochure (IB), 15th Edition.

MAPPUSX Protocol Synopsis

Full protocol begins on Page 8.

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 and 3 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 safety extension study is intended to explore the safety and effectiveness of MDMA-assisted therapy for the treatment of PTSD.

Study Design

This multi-site open-label safety extension study of MDMA-assisted therapy for the treatment of participants with PTSD will be conducted in N≈100 participants, by invitation only.

The treatment consists of a flexible dose of MDMA, followed by a supplemental dose unless tolerability issues emerge, administered with therapy in three open-label approximately monthly Experimental Sessions. This Treatment Period is preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session is followed by three Integrative Sessions of non-drug therapy. Experimental Sessions are followed by an overnight stay; a sub-study (Appendix A) will assess feasibility of Experimental Sessions without an overnight stay. The Primary Outcome measure, the change in PCL-5 (PTSD Checklist for DSM-5) from Visit 3 is assessed at Visit 16. An independent Data Monitoring Committee (DMC) will review safety data as described in the DMC charter and at any time a Serious Adverse Reaction (SAR) occurs (refer to Section 10.5 Data Monitoring Committee).

For each participant, the study will consist of:

- **Screening Period**: phone screen, informed consent, eligibility assessment, and enrollment of eligible participants
- **Preparatory Period**: medication tapering, Preparatory Sessions
- **Treatment Period**: three monthly Experimental Sessions over up to 4 months, followed by Integrative Sessions
- **Study Termination**: Primary Outcome PCL-5 4 weeks after third Experimental Session
- **Invitation to participate in Long-term Follow-up (LTFU) extension study**: at least 6 months after last Experimental Session

Primary Outcome (PCL-5) Data Collection by Visit

PCL-5 Number	Visit	Description/Timing
Initial PCL-5 T0	Screening	Prior to enrollment and initiation of tapering
Baseline PCL-5 T1	V3	Baseline After tapering and stabilization, at Preparatory Session 3 (Visit 3)
PCL-5 T2	V6	10 to 18 days after Experimental Session 1 At Integrative Session 1.2 (Visit 6)
PCL-5 T3	V10	10 to 18 days after Experimental Session 2 At Integrative Session 2.2 (Visit 10)
PCL-5 T4	V14	10 to 18 days after Experimental Session 3 At Integrative Session 3.2 (Visit 14)
Primary Outcome PCL-5 T5	V16	24 to 32 days after Experimental Session 3 At Study Termination (Visit 16)

Dose Selection

This open-label study will examine the safety and effectiveness of a flexible dose of MDMA administered in three Experimental Sessions, 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 Phase 3 studies sponsored by MAPS.

Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	80 or 120 mg	40 or 60 mg	80 mg to 180 mg
3	80 or 120 mg	40 or 60 mg	80 mg to 180 mg
		Total Cumulative Dose	240 mg to 480 mg

* Unless tolerability issues emerge with the first dose or it is refused by the participant.

Protocol Objective

The overall objective of this study is to use standard clinical measures to explore the safety and effectiveness of MDMA-assisted therapy with a flexible dose of MDMA in reducing PTSD and associated symptoms.

Primary Objective

The primary objective of this study is to evaluate the effectiveness of MDMA-assisted therapy for PTSD, as measured by the reduction in PCL-5 total score from Visit 3 to Visit 16.

Secondary Objective

The key secondary objective of this study is to evaluate the effectiveness of MDMA-assisted therapy for PTSD in functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 to Visit 16.

Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of Adverse Events (AEs), Treatment Emergent AEs (TEAEs), AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, 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 Medicinal Product (IMP) 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 TEAEs by severity
4. Assess incidence of TEAEs by severity reported during an Experimental Session, 1 day, and 2 days after IMP administration
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function, suicidality, and abuse liability
6. Assess incidence of AEs by severity categorized as leading to discontinuation of IMP, resulting in death or hospitalization, and continuing at Study Termination
7. Assess incidence of SAEs
8. Assess incidence of concomitant medications taken during an Experimental Session, 1 day, and 2 days after IMP administration
9. Assess incidence of psychiatric concomitant medications taken during the Treatment Period
10. Assess incidence of positive or serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS)
11. Assess changes in blood pressure (BP), heart rate, and body temperature from pre-IMP administration to end of each Experimental Session

Recruitment and Participant Population

Approximately N≈100 participants will be enrolled, by invitation only. Participants who were randomized to the placebo arm in the two parent Phase 3 trials and who meet all other entry criteria will be eligible and invited to participate in this open-label safety extension study. In addition, participants in the parent Phase 3 trials whose study participation was affected by the Coronavirus 2019 (COVID-19) global pandemic or other unforeseen circumstances, and were unable to complete the study (enrolled but not treated or enrolled, treated, but could not complete three Experimental Sessions prior to termination of the study) may participate in this open-label study if they meet all eligibility criteria and are approved by the Medical Monitor.

Participants will be 18 years or older, considered in good standing with the study site at which they enrolled in a parent study, and able to agree to lifestyle modifications. 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 must be in good physical health and without major medical disorders that could affect the safety or tolerability of MDMA.

Statistical Analyses

This is a multi-site open-label safety extension study of MDMA-assisted therapy for the treatment of participants with PTSD. The effectiveness of MDMA-assisted therapy will be measured by the PCL-5 and SDS. The sample size was not determined by statistical criteria. Every effort will be made to ensure (i) complete, accurate, and timely data collection and to avoid missing data, and (ii) the completeness of the data, which can impact the integrity and accuracy of the final study analysis. The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS® Version 9.4. In general, nominal variables will be described in terms of frequencies and percentages. Ordinal and non-parametric continuous variables will be described using the sample median, 25th and 75th percentiles, and the interquartile range (IQR).

The following analysis set is defined for this study:

- **All Enrolled**: all participants who were enrolled in the study
- **Safety**: all participants who received any IMP

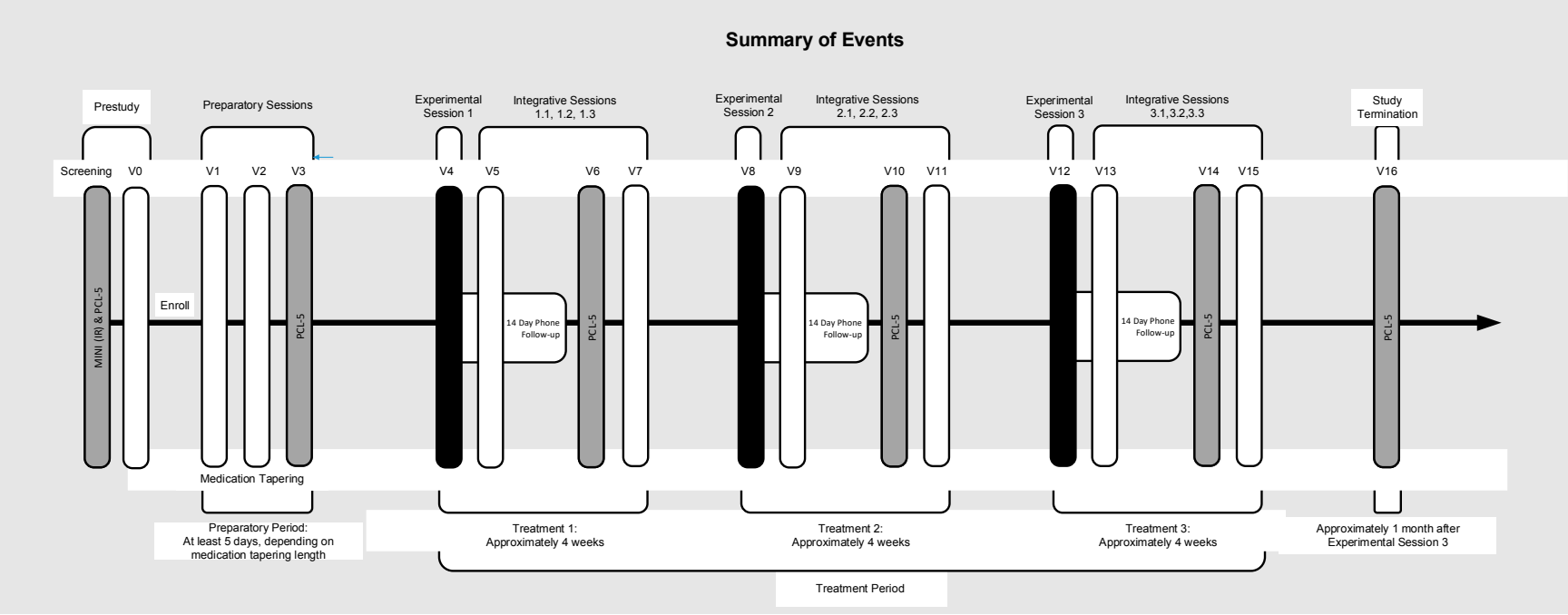
Primary Effectiveness Analysis

The primary analysis of the effectiveness of MDMA-assisted therapy will be made using a Mixed Model Repeated Measure (MMRM) model to assess changes in PCL-5 scores throughout the study period from Baseline (Visit 3) through Visit 16. Baseline covariates (age, gender, ethnicity, index trauma, complexity and severity of trauma, diagnosis of comorbid depression, diagnosis of comorbid Axis 2 diagnosis, adverse childhood experiences collected in the parent study) may be assessed for inclusion in the final model with an alpha level set at 0.05. Details of the analysis are described in the Statistical Analysis Plan.

Secondary Effectiveness Analysis

The SDS will be analyzed in a similar manner to the primary analysis of the PCL-5. Please refer to the Statistical Analysis Plan for more details.

Study Structure Overview



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List of Abbreviations

°C	Degrees Celsius
A: G	Albumin: Globulin
ADHD	Attention Deficit/Hyperactivity Disorder
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	American Heart Association
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
API	Active Pharmaceutical Ingredient
ASA	American Stroke Association
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BDI-II	Beck Depression Inventory-II
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAPS-4	Clinician-Administered PTSD Scale for DSM-4
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
cGMP	Good Manufacturing Practice
CMC	Chemistry Manufacturing and Control
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
DMC	Data Monitoring Committee
DSM-4	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSP-I	Dissociative Subtype of PTSD Interview
DUDIT	Drug Abuse Disorders Identification Test
EAT-26	Eating Attitudes 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
ESC	European Society of Cardiology
EQ-5D-5L	EuroQol Five Dimensions-Five Levels Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability
HIV	Human Immunodeficiency Virus

HPA	Hypothalamic-pituitary-adrenal
HPMC	Hydroxypropyl Methylcellulose
HPQSF	Health and Work Performance Absenteeism and Presenteeism Short Form
IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IR	Independent Rater
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IWRS	Interactive Web Randomization 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
mg	Milligram
MINI	Mini-International Neuropsychiatric Interview
mITT	Modified Intent-to-Treat
mmHg	Milligrams of Mercury
MMRM	Mixed Model Repeated Measure
MPBC	MAPS Public Benefit Corporation
ms	Millisecond
PABP	Participant able to become pregnant
PCL-5	PTSD Checklist for DSM-5
PHI	Protected Health Information
PTSD	Posttraumatic Stress Disorder
PVC	Premature Ventricular Contraction
RACT	Risk Assessment and Categorization Tool
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SDS	Sheehan Disability Scale
SGOT	Serum Glutamic Oxaloacetic Transaminase
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SRNU	Self-reported Nicotine Use
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

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 (MPBC).

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.

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 justified confirmation in a Phase 3 program to further assess the efficacy and safety of this treatment for participants with at least moderate PTSD. The sponsor completed two Phase 3 randomized, placebo-controlled, two-arm, double-blind, multi-site studies of three once-monthly Experimental Sessions of therapy combined with either a flexible dose of MDMA or placebo, along with non-drug preparatory and integrative therapy.

Participants who were randomized to the placebo arm in either of the two parent Phase 3 trials and who meet all other entry criteria will be eligible and invited to participate in this open-label safety extension study. In addition, participants in the parent Phase 3 trials whose study participation was affected by the Coronavirus 2019 (COVID-19) global pandemic or other unforeseen circumstances and were unable to complete the study (enrolled but not treated or enrolled, treated, but could not complete three Experimental Sessions prior to termination of the study) may participate in this open-label study. This study will follow a similar schedule of events as the Phase 3 protocols but will measure PTSD severity using a self-report measure, the PTSD Checklist (for Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-5]) (PCL-5).

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 [1]. The four main symptom categories described in the DSM-5, include arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and nightmares [2]. 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 [3-5]. People who suffer from PTSD often relive the experience through nightmares and

flashbacks, have poor sleep quality, and feel detached or estranged [6]. 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 [7]. 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 [7]. 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 [8, 9]. 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 [10]. 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 [11]. 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 [12]. There are an estimated 20 to 22 suicides a day by veterans [13].

Available PTSD treatments, including medications and therapy, effectively treat only a fraction of people who try them for adequate dose and duration. This indicates a need to develop treatments targeting durable remission of PTSD. 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 Clinician Administered PTSD Scale (CAPS) in 12-week confirmatory clinical trials with daily dosing, but some studies were less effective in treating combat-related PTSD and sertraline demonstrated gender differences with minimal efficacy in men [14-16]. PTSD rarely remits after 12 weeks of SSRIs, and many patients who are placed on maintenance treatment experience partial relief of symptoms, which fully return upon discontinuation of treatment. Adverse effects of maintenance SSRI treatment that contribute to discontinuation include sexual dysfunction, weight gain, and sleep disturbance. Variable SSRI treatment outcomes have led to recommendations of trauma-focused psychotherapy 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 [17, 18]. 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 indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and eye

movement desensitization and reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD [19, 20], 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" psychotherapies, including those listed above, are similarly effective with PTSD [21]. In the past decade, there has been a growing amount of research into medications and other methods that may augment the effectiveness of psychotherapy for PTSD (see [22] for a review). Examples of this are virtual reality-assisted exposure therapy [23, 24] and D-cycloserine-assisted psychotherapy [25]. 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 [26, 27]. Similar to SSRIs, MDMA binds to the serotonin transporter, but has additional effects on carrier-mediated release and reuptake inhibition of norepinephrine and to a lesser extent in humans, dopamine [28-34]. MDMA also increases levels of affiliative neurohormones oxytocin and vasopressin, which increases trust and attenuates reactivity to threatening cues, and some researchers have suggested a role for oxytocin in treating PTSD. The indirect effects of MDMA on central and peripheral neurohormone release contribute to a novel mechanism that may help regulate the HPA axis, which would treat the core psychopathology of PTSD for a durable remission.

Onset of MDMA effects occurs ~0.5 to 1 hour after oral administration, and peak effects occur 1.25 to 2 hours after the initial dose. Effects of the initial dose last 3 to 6 hours, with most effects returning to baseline or near-baseline levels 6 hours after final drug administration [35-37]. 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) [38, 39]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [40]. 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 psychotherapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in psychotherapy with an appropriate level of emotional engagement [20]. To be effective, exposure must be accompanied by a degree of emotional engagement or "fear activation" while avoiding dissociation or overwhelming emotion [41]. This has been referred to as working within the "optimal arousal zone" or "window of tolerance" [42-44].

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, causing heightened encoding of fearful memories and decreasing blood flow in the prefrontal cortex. In contrast, MDMA acutely decreases activity in the amygdala [45], and there is some indication that MDMA may increase activity in the prefrontal cortex [46]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [45]. This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [47-49]. 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 [50-53]. 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 [54]. 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 Therapy, which the sites and therapy teams 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 [55], with 80 to 160 milligrams (mg) MDMA required to produce desired subjective effects in humans [55, 56]. MDMA was found to robustly influence human emotional status in a unique way [55] without adversely affecting physiological functions or perception, such as visual perception or cognition [35, 37, 57, 58]. In the 1970s, psychotherapists used MDMA-assisted therapy to treat psychological disorders, including anxiety [59]. Legal therapeutic use continued until its placement on the U.S. list of Schedule I substances in 1985 [51, 54, 60]. An estimated 500,000 doses of MDMA were administered during psychotherapy and personal growth sessions in North America prior to its scheduling [51, 61]. A few uncontrolled human studies of MDMA assessing safety in a therapeutic setting occurred in the 1980s [62, 63].

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 [64, 65]. 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 [53]. 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 (Clinician-Administered PTSD Scale for DSM-4 [CAPS-4] 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 two 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 (MP1) [52, 66] and one in Switzerland (MP2) [67, 68]. MP1 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 (MP1E2). Three additional studies have completed treatments (MP8, MP9, MP12) and two international studies were terminated early for logistical reasons with partial datasets (MP3, MP4). These studies tested a range of designs, such as a placebo control (MP1, MP4), low dose MDMA comparator control (MP2, MP9), and three-arm dose response studies (MP8, MP12). MP4 was terminated early due to delays in regulatory approval and enrollment timelines, with available efficacy data presented without a formal analysis. MP3 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 (MP3 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 (MP1, MP2, MP4, MP8, MP9, MP12) consisting of 107 blinded participants with chronic PTSD was completed in 2016. In these studies, PTSD, independent of cause, appears treatable with a two to three-session treatment package of MDMA-assisted therapy. Durable improvements were found at least 12 months after the last Experimental Session in 91 participants who received a therapeutically active dose of MDMA in these studies, and 67% did not meet PTSD diagnostic criteria per CAPS-4 assessment [69]. As of October 01, 2022, with 426 individuals exposed to MDMA in the sponsor's development program across various indications and at least 1,548 participants in MDMA research studies conducted without sponsor support (for a total of at least 1,974 individuals), the sponsor has observed an acceptable risk-benefit ratio for MDMA-assisted therapy. Across Phase 2 studies, 75 mg-125 mg MDMA was statistically superior to 0 mg to 40 mg MDMA based on a t-test of difference in CAPS-4 severity scores from Baseline, 2 months after two blinded Experimental Sessions ($p<0.001$). The dropout rate across studies was 7.5% (8 of 107). Large between-groups effect size estimates (0.9), initial indications of efficacy, and favorable safety outcomes support expanding the research initiative to encompass a larger sample of participants with PTSD in a Phase 3 program. The first randomized, double-blind, placebo-controlled multi-site Phase 3 study for MDMA-assisted therapy for severe PTSD in the United States, Canada and Israel had a total of 90 randomized participants (46 randomized to MDMA and 44 to placebo). 67% of the participants in the MDMA group no longer met the diagnostic criteria for PTSD after 3 experimental sessions as confirmed by the change in CAPS-5 total severity score [70]. An identical randomized, double-blind, placebo-controlled multi-site Phase 3 study confirming the efficacy and safety of MDMA-assisted therapy for the treatment of PTSD was recently concluded.

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 safety and effectiveness of MDMA-assisted therapy with a flexible dose of MDMA in reducing PTSD and associated symptoms.

2.1 Primary Objective

The primary objective of this study is to evaluate the effectiveness of MDMA-assisted therapy for PTSD, as measured by the reduction in PCL-5 total score from Visit 3 to Visit 16.

2.2 Key Secondary Objective

The key secondary objective of this study is to evaluate the effectiveness of MDMA-assisted therapy for PTSD in functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 to Visit 16.

2.3 Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of Adverse Events (AEs), Treatment Emergent AEs (TEAEs), AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, 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 Medicinal Product (IMP) 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 TEAEs by severity
4. Assess incidence of TEAEs by severity reported during an Experimental Session, 1 day, and 2 days after IMP administration
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function, suicidality, and abuse liability
6. Assess incidence of AEs by severity categorized as leading to discontinuation of IMP, resulting in death or hospitalization, and continuing at Study Termination
7. Assess incidence of SAEs
8. Assess incidence of concomitant medications taken during an Experimental Session, 1 day, and 2 days after IMP administration
9. Assess incidence of psychiatric concomitant medications taken during the Treatment Period
10. Assess incidence of positive or serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS)
11. Assess changes in blood pressure (BP), heart rate, and body temperature from pre-IMP administration to end of each Experimental Session

2.4 Exploratory Objectives

These objectives may be explored to characterize participants receiving MDMA-assisted therapy to support the primary objective:

1. Explore the effect of presence of secondary traumatic stressors identified on the Life Events Checklist (LEC-5) on the PCL-5 total severity analysis
2. Explore differences from Visit 3 to Visit 16 in:
    a. Depression (BDI-II)
    b. Chronic pain (CPGS)
    c. Quality of life (EQ-5D-5L)
    d. Nicotine use (SRNU)
    e. Eating habits (EAT-26)
    f. Workplace productivity (HPQSF)
3. Explore differences from Screening to Visit 16 in alcohol use (AUDIT) and drug use (DUDIT)

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.

In the below criteria, "parent study" refers to a MAPS-sponsored Phase 3 clinical trial of MDMA-assisted therapy, namely MAPP1 or MAPP2.

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

1. Were previously enrolled in a parent study, met all criteria in the parent study at the time of enrollment in the parent study, and (meet one of the following):
    a. At time of unblinding, their treatment assignment was to the placebo arm; or,
    b. Did not begin Experimental Sessions due to the COVID-19 global pandemic or other unforeseen circumstances; or,
    c. Completed fewer than three Experimental Sessions prior to Study Termination due to the COVID-19 global pandemic or other unforeseen circumstances.
2. Are considered in good standing with the study site at which they enrolled in a parent study; if, in the opinion of the investigator, therapy team, and Medical Monitor, the participant was compliant with protocol requirements, even if they were unable to complete all study visits.
3. Are at least 18 years old.
4. Are fluent in speaking and reading the predominantly used or recognized language of the study site.
5. Are able to swallow pills.
6. Agree to have study visits recorded, including Experimental Sessions and non-drug therapy sessions.
7. 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.
8. Must agree to inform the investigators within 48 hours of any medical conditions and procedures.
9. For participants assigned female sex at birth:
    - A participant is eligible to participate if not pregnant, and one of the following conditions applies:
        - Is not able to become pregnant as defined in Section 10.3.1 Definition of Able to Become Pregnant.

        OR
        - Is a person able to be pregnant (PABP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.3.2 Contraception Guidelines, during the study intervention period and for at least 10 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance or drug interactions with oral contraception [e.g., antibiotics], recently initiated) in relationship to the first dose of study intervention. PABP who are taking oral contraception and antibiotics, or other medications known to decrease the effectiveness of oral contraception, should be counseled to use a barrier method of birth control as well as oral contraception for the duration of the antibiotic or other drug interaction and for 10 days thereafter.
    - A PABP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at study entry and prior to each experimental session.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.

10. 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 commit to medication dosing, therapy, and study procedures.

Medical History

11. At time of enrollment, met all inclusion and no exclusion criteria in parent study.
12. 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.
13. May have asymptomatic Hepatitis C virus (HCV) that has previously undergone evaluation and treatment as needed.
14. May have current mild or moderate alcohol or cannabis use disorder (meets 3 to 5 of 11 diagnostic criteria per DSM-5).
15. 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.
16. May have hypothyroidism if taking adequate and stable thyroid replacement medication.
17. 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 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.
3. Have any current problem which, in the opinion of the investigator or Medical Monitor, might interfere with participation.

Psychiatric History

4. Have received Electroconvulsive Therapy (ECT) within 12 weeks of enrollment.
5. Have a history of or a current primary psychotic disorder, bipolar disorder 1 assessed via MINI and clinical interview.
6. Have a current eating disorder with active purging assessed via MINI and clinical interview.
7. Have current major depressive disorder with psychotic features assessed via MINI.
8. Have a current severe alcohol or cannabis use disorder within the 12 months prior to enrollment (meets at least 6 of 11 diagnostic criteria per DSM-5).
9. Have an active illicit (other than cannabis) or prescription drug substance use disorder at any severity within 12 months prior to enrollment.
10. 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.

11. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist.
12. Require ongoing concomitant therapy with a psychiatric medication with exceptions described in Section 11.0 Concomitant Medications.

Medical History

13. 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 or Medical Monitor to significantly increase the risk of MDMA administration by any mechanism would require exclusion.
14. 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).
15. Have a history of ventricular arrhythmia at any time, other than occasional premature ventricular contractions (PVCs) in the absence of ischemic heart disease.
16. Have Wolff-Parkinson-White syndrome or any other accessory pathway that has not been successfully eliminated by ablation.
17. Have a history of arrhythmia, other than occasional PACs or PVCs in the absence of ischemic heart disease, within 12 months of screening. Participants with a history of atrial fibrillation, atrial tachycardia, atrial flutter or paroxysmal supraventricular tachycardia or any other arrhythmia associated with a bypass tract may be enrolled only if they have been successfully treated with ablation and have not had recurrent arrhythmia for at least 1 year off all antiarrhythmic drugs, or are under adequate and stable pharmacologic treatment for atrial fibrillation for at least a year, as confirmed by a cardiologist.
18. Have a marked Baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTcF interval>450 milliseconds [ms] in males and>460 ms in females corrected by Fridericia's formula). For transgender or non-binary participants, QTcF interval will be evaluated based on sex assigned at birth, unless the participant has been on hormonal treatment for five or more years. Participants whose QTcF exceeds this value during screening may be enrolled if a pre-study concomitant medication is suspected to be prolonging the QT-interval. ECGs should be repeated after tapering off the pre-study concomitant medication to ensure the participant meets eligibility criteria prior 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.

19. Have a history of additional risk factors for *Torsade de pointes* (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
20. Require use of concomitant medications that prolong the QT/QTc interval during Experimental Sessions. Refer to Section 11.0 Concomitant Medications.
21. Have symptomatic liver disease or have significant liver enzyme elevations.
22. Have a recent history of clinically significant hyponatremia or hyperthermia.
23. Weigh less than 48 kilograms (kg).
24. 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.

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.
- Agree not to use alcohol or cannabis after 12:00 A.M. (midnight) before 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 opioids (per Section 11.0 Concomitant Medications), if used for pain management, leading up to the Experimental Session in order to avoid taking the medication for at least 12 hours prior to the initial IMP administration and 24 hours after. During this period, the participant will be allowed to take the medication if needed for intolerable pain flare-ups or to prevent withdrawal symptoms.
- Agree that, for 1 week preceding each Experimental Session to 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 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 contraception, thyroid hormones, anti-hypertensives, or other medications approved by the research team).

Post Experimental Session (for exceptions, see Appendix A)

- 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 after each Experimental Session until after the Integrative Session the next morning.

4.0 Protocol Design

4.1 Study Design Overview

This multi-site open-label safety extension study of MDMA-assisted therapy for the treatment of participants with posttraumatic stress disorder will be conducted in N≈100 participants, by invitation only.

For each participant, the study will consist of:

- **Screening Period**: phone screen, informed consent, eligibility assessment, and enrollment of eligible participants
- **Preparatory Period**: medication tapering, Preparatory Sessions
- **Treatment Period**: three monthly Experimental Sessions over up to 4 months, followed by Integrative Sessions
- **Study Termination**: Primary Outcome PCL-5 4 weeks after third Experimental Session
- **Invitation to participate in Long-term Follow-up (LTFU) extension study**: at least 6 months after last Experimental Session

The treatment consists of a flexible dose of MDMA, followed by a supplemental dose unless tolerability issues emerge, administered with therapy in three open-label approximately monthly Experimental Sessions. This Treatment Period is preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session is followed by three Integrative Sessions of non-drug therapy. Experimental Sessions are followed by an overnight stay; a sub-study (Appendix A) will assess feasibility of Experimental Sessions without an overnight stay. The Primary Outcome measure, the change in PCL-5 from Visit 3, is assessed at Visit 16.

Figure 1: Study Structure Overview

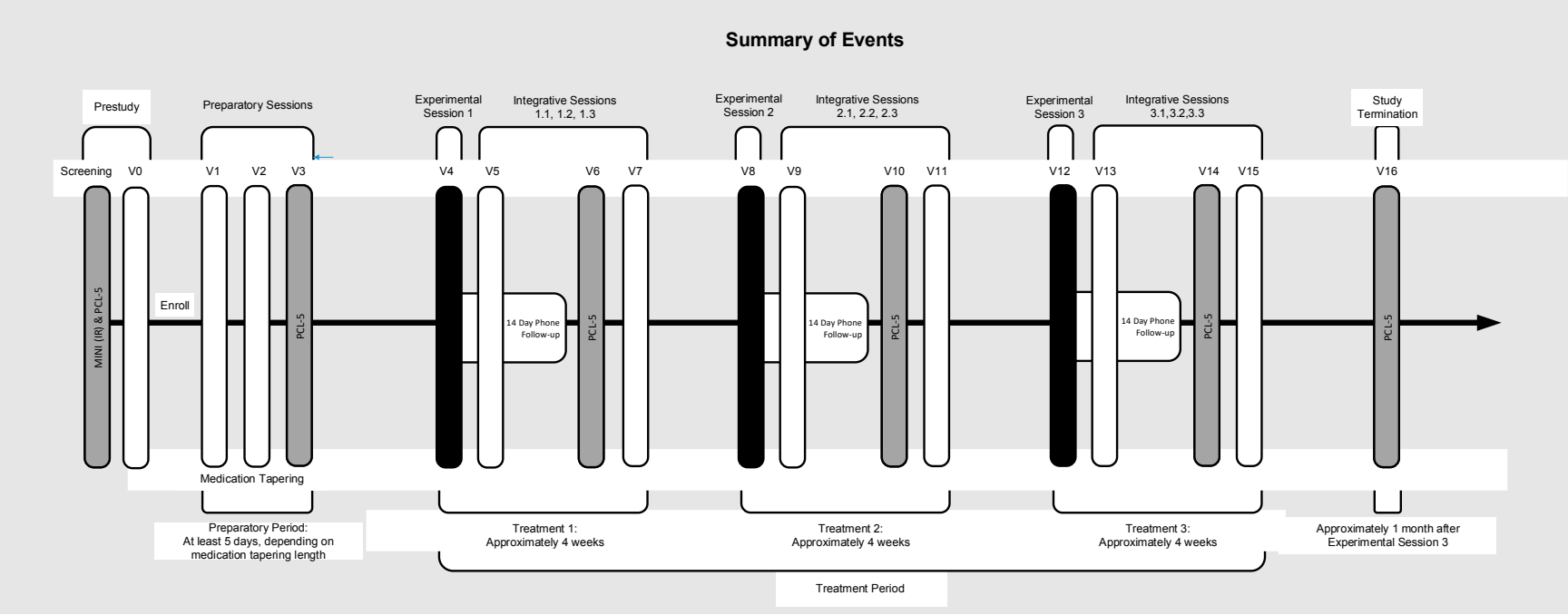

Table 1: Study Design Overview

Screening Period From Consent to Enrollment (Visit 0): 1 to 10 weeks			
Study Visit		**Visit Duration/ Visit Timing**	**Brief Description of Events**
Screening	Screening	Multiple visits over 7 to 70 days/ After phone screen	At initial visit, obtain Informed Consent and assess all screening measures (including PCL-5 and Interim C-SSRS), interim medical history, and interim and current medications. Contact outside providers and order medical records (as needed), physical exam, labs (including pregnancy and drug tests), ECG, and 1-minute rhythm strip. Once all results are obtained, review along with notes from all screening visits and measures. If eligible, send results of LEC-5 & C-SSRS to IR.
	Independent Rater Screening	1 hour/ After initial screening visit	After initial eligibility is reviewed, an IR will conduct the MINI and C-SSRS via telemedicine. Results will be confirmed by clinical observation during the Preparatory Period, but the MINI will not be repeated.
Enrollment	Enrollment (Visit 0)	1.5 hours/ 2 to 14 days after Independent Rater Screening	Prior to enrolling: review all screening measures, medical history, discussion with outside providers and sponsor, and any clarification phone calls with participant. Visit is 1.5 hours to review eligibility and medical tapering plan. If enrolled, begin taper, followed by five half-lives of drug or active metabolite (whichever is longer), (for stabilization prior to V3). For non-selective irreversible MAOIs, a 2-week washout period following the taper is required (3 weeks in the case of imipramine and clomipramine, tricyclic antidepressants with MAOI activity).

Preparatory Period From Preparatory Session 1 (Visit 1) to Preparatory Session 3 (Visit 3): 1 to 11 weeks			
Study Visit/ Visit #		**Visit Duration/ Visit Timing**	**Brief Description of Events**
Preparatory Period	Preparatory Session 1 (Visit 1)	1.5 hours/ 0 to 14 days after Enrollment (V0)	90-minute Preparatory Session. Target visit timing on tapering needs. If needed, schedule calls between Visits 1 and 2 if indicated for tapering, safety, or further questions about medical history or eligibility.
	Preparatory Session 2 (Visit 2)	1.5 hours/ 2 to 75 days after V1	90-minute Preparatory Session. If tapering is complete or not needed, check eligibility and schedule Visits 3 and 4. If tapering is ongoing, schedule post taper call for ongoing assessment.
	Phone Call End Taper	1 hour/ 0 to 7 days after taper and stabilization end; up to 77 days after V0	If needed, confirm medication taper and stabilization is complete. Medication taper for psychoactive 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.
	Preparatory Session 3 Baseline PCL-5 T1 (Visit 3)	1.5 hours/ As soon as possible post V2 & Medication Taper; 1 to 14 days before V4	90-minute Preparatory Session. PCL-5, SDS, C-SSRS, and exploratory measures collected by study team.

Treatment Period From Experimental Session 1 (Visit 4) to Integrative Session 3.3 (Visit 15): 6 to 20 weeks			
Study Visit/ Visit #		**Visit Duration/ Visit Timing**	**Brief Description of Events**
Treatment 1	Experimental Session 1 (Visit 4)	At least 6 hours + overnight/ 1 to 14 days after V3	First Experimental Session occurs 1 to 14 days after Preparatory Session 3 (Visit 3), it lasts at least 6 hours with overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless tolerability issues emerge with the first dose or it is refused by the participant. C-SSRS administered pre- and post- Investigational Product administration.
	Integrative Session 1.1 (Visit 5)	1.5 hours/ Morning after V4	90-minute Integrative Session the morning after Visit 4. Followed by phone check-ins every other day for 14 days. C-SSRS administered during Integrative Session 1.1 and phone calls.
	Integrative Session 1.2 (Visit 6)	1.5 hours/ 10 to 18 days after V4; at least 2 days after V5	Between 10 and 18 days after Visit 4, a 90-minute Integrative Session is completed. C-SSRS, PCL-5, and LEC-5 are administered.
	Integrative Session 1.3 (Visit 7)	1.5 hours/ at least 2 days after V6; 1 to 14 days before V8	90-minute Integrative Session at least 2 days after Integrative Session 1.2 (Visit 6) and 1 to 14 days before Experimental Session 2 (Visit 8). C-SSRS administered.
Treatment 2	Experimental Session 2 (Visit 8)	At least 6 hours + overnight/ 21 to 56 days after V4; 1 to 14 days after V7	Second Experimental Session occurs 1 to 14 days after Integrative Session 1.3 (Visit 7), it lasts at least 6 hours with overnight stay. Dose is 80 or 120 mg plus supplemental dose unless tolerability issues emerge with the first dose or it is refused by the participant. C-SSRS administered pre-and post-Investigational Product administration.
	Integrative Session 2.1 (Visit 9)	1.5 hours/ Morning after V8	90-minute Integrative Session the morning after Visit 8. Followed by phone check-ins every other day for 14 days. C-SSRS administered during Integrative Session 2.1 and phone calls.
	Integrative Session 2.2 (Visit 10)	1.5 hours/ 10 to 18 days after V8; at least 2 days after V9	Between 10 and 18 days after Visit 8, a 90-minute Integrative Session is completed. C-SSRS, PCL-5, and LEC-5 are administered.
	Integrative Session 2.3 (Visit 11)	1.5 hours/ at least 2 days after Integrative Session 2.2 (Visit 10) 1 to 14 days before V12	90-minute Integrative Session at least 2 days after Integrative Session 2.2 (Visit 10) and 1 to 14 days before Experimental Session 3 (Visit 12). C-SSRS administered.
Treatment 3	Experimental Session 3 (Visit 12)	At least 6 hours + overnight/ 21 to 56 days after V8; 1 to 14 days after V11	Third Experimental Session occurs 1 to 14 days after Integrative Session 2.3 (Visit 11), it lasts at least 6 hours with overnight stay. Dose is 80 or 120 mg plus supplemental dose unless tolerability issues emerge with the first dose or it is refused by the participant. C-SSRS administered pre- and post-Investigational Product administration.
	Integrative Session 3.1 (Visit 13)	1.5 hours/ Morning after V12	90-minute Integrative Session the morning after Visit 12. Followed by phone check-ins every other day for 14 days. C-SSRS administered during Integrative Session 3.1 and phone calls.
	Integrative Session 3.2 (Visit 14)	1.5 hours/ 10 to 18 days after V12; at least 2 days after V13	Between 10 and 18 days after Visit 12, a 90-minute Integrative Session is completed. C-SSRS, PCL-5, and LEC-5 are administered.
	Integrative Session 3.3 (Visit 15)	1.5 hours/ At least 2 days after V14	90-minute Integrative Session at least 2 days after Integrative Session 3.2 (Visit 14). C-SSRS administered.

Study Termination From Experimental Session 3 (Visit 12) until Study Termination (Visit 16): 24 to 32 days			
Study Visit/ Visit #		**Visit Duration/ Visit Timing**	**Brief Description of Events**
Primary Outcome Study Termination	Primary Outcome PCL-5 T5 Study Termination (Visit 16)	2 hours/ 24 to 32 days after V12	Primary Outcome PCL-5 and LEC-5 completed. Complete self-reported and safety measures. Create an exit plan for participant. Collect weight and final blood pressure. Invite participant to the extension study for LTFU.

Table 2: Primary Outcome (PCL-5) Data Collection by Visit

PCL-5 Number	Visit	Description/Timing
Initial PCL-5 T0	Screening	Prior to enrollment and initiation of tapering
Baseline PCL-5 T1	V3	Baseline After tapering and stabilization, at Preparatory Session 3 (Visit 3)
PCL-5 T2	V6	10 to 18 days after Experimental Session 1 At Integrative Session 1.2 (Visit 6)
PCL-5 T3	V10	10 to 18 days after Experimental Session 2 At Integrative Session 2.2 (Visit 10)
PCL-5 T4	V14	10 to 18 days after Experimental Session 3 At Integrative Session 3.2 (Visit 14)
Primary Outcome PCL-5 T5	V16	24 to 32 days after Experimental Session 3 At Study Termination (Visit 16)

4.2 Planned Duration of Study

Full screening may take 70 days after Informed Consent is obtained during the Informed Consent visit. The Preparatory Period begins at enrollment and can be as brief as 5 days but depending on medication tapering could be as long as necessary to ensure an appropriate medication washout. An appropriate psychoactive medication taper schedule should be defined by the treating physician. The taper will be followed by a washout period of five half-lives of drug or active metabolite (whichever is longer). For non-selective irreversible MAOIs, a 2-week washout period following the taper is required (3 weeks in the case of imipramine and clomipramine, tricyclic antidepressants with MAOI activity). The taper followed by washout should be completed for psychological stabilization prior to Baseline PCL-5 (Visit 3). Medication taper for psychoactive medications should occur prior to Visit 3. Medication taper for medications with drug-drug interactions without a psychiatric concern should occur prior to Visit 4. The Treatment Period will consist of three Experimental Sessions 3 to 8 weeks apart with associated non-drug Integrative Sessions.

Four weeks after the final Experimental Session 3 (Visit 12) and after the final Integrative Session 3.3 (Visit 15), participants will complete Study Termination (Visit 16), including administration of the Primary Outcome PCL-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, and the maximum is dependent on medication tapering. The average participant is expected to complete the study in 22 weeks. 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.

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.

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

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

- Preparatory and Integrative Visits may be conducted by 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 or initiating 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.

4.4 Discontinuation and Completion Criteria

4.4.1 Complete or Evaluable Participants

A participant is considered ‘Evaluable’ and eligible for the Modified Intent-to-Treat (mITT) analysis if they have completed at least one Experimental Session and one PCL-5 assessment beyond Baseline.

A participant is considered ‘Evaluable and Completed Per Protocol’ if they have completed all Experimental Sessions and PCL-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 PCL-5 assessment beyond Baseline but terminated early from treatment. 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, they will be classified as a Screen Failure. The site staff will notify the potential participant that they are unfortunately not eligible for the study and will 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 an outside therapist if needed. Screen Failures will be entered into the Electronic Data Capture (EDC) system.

4.4.3 Pre-Treatment Early Terminations

'Pre-Treatment Early Terminations' are defined as participants who were deemed eligible and enrolled in the study at Visit 0, but are deemed ineligible prior to the first Experimental Session. These participants may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to the first Experimental Session or the site may withdraw the participant for reasons described in Section 4.4.4 Early Termination from the Study). All enrolled participants will be maintained in the EDC system. Pre-Treatment Early Terminations are not considered evaluable.

Pre-Treatment Early Terminations may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the participant. At any time during the Preparatory Period, if a potential participant is deemed to be ineligible, the site staff will classify as a Pre-Treatment Early Termination, notify the potential participant that they are unfortunately not eligible for the study, and not schedule additional assessments. Pre-Treatment Early Terminations will be provided an Exit Plan/Plan for Moving Forward as described in Section 7.4.2 Exit Plan/Plan for Moving Forward.

4.4.4 Early Termination from the Study

Participants who are removed from the study after they receive IMP but do not complete the study may fall into one of these categories: Post-Treatment Early Termination or Dropout. If the participant has received IMP in at least one Experimental Session and completed one PCL-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 Electronic Case Report Form (eCRF). If a participant develops any Exclusion Criteria that, in the opinion of the Medical Monitor or Investigators, affects the safety of the participant, including psychiatric diagnosis, medical diagnosis, pregnancy, or requirement of use of prohibited medications, the participant will discontinue treatment in Experimental Sessions but remain in the study for the associated Integrative Sessions. 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 an Exit Plan/Plan for Moving Forward as described in Section 7.4.2 Exit Plan/Plan for Moving Forward.

Below are the definitions of the two types of participants who terminate the study after they receive IMP but before study completion:

- **Post-Treatment Early Termination**: Participants who discontinue study treatment but continues to participate in primary and secondary outcome assessments. Data collection 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 PCL-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.

4.4.5 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 PCL-5 assessment after the Experimental Session, 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.

If at a later date it is determined that the participant was lost to follow-up due to an SAE, AESI or pregnancy, then the investigator should report this within 24 hours of discovery to the Sponsor.

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 5: Time and Events 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 Exit Plan/Plan for Moving Forward. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with federal and state regulations.

4.6 Rationale of Dose Selection

Similar MDMA doses to those proposed in this study have been 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 selection of a 3-session treatment package. A flexible dosing regimen has been explored previously in Phase 2 studies, where participants who received doses of 0 mg to 75 mg MDMA in the blinded portion of the study crossed over to receive open-label 100 mg MDMA in the first Experimental Session with an option to increase to 125 mg MDMA in the second and third Experimental Sessions. Larger doses have been administered 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. In the first Phase 3 trial, participants received a single divided dose of 80-180mg of MDMA or placebo. In the first experimental session, an initial dose of 80 mg was followed by a supplemental half-dose of 40 mg 1.5–2.5 h after the first dose. In the second and third experimental sessions, there was the option to increase to an initial dose of 120 mg was followed by a supplemental half-dose of 60 mg. This dosing regimen produced an appropriate response with no tolerability issues.

This open-label study will examine the effectiveness of a flexible dose of MDMA administered in three Experimental Sessions. A participant will receive a divided-dose of 120 mg or 180 mg per Experimental Session. The dose regimen will match that of the parent studies. Initial doses per Experimental Session are 80 mg or 120 mg of MDMA compounded with inactive excipients, followed 1.5 to 2 hours later by a supplemental dose (40 mg or 60 mg). A flexible dosing regimen was chosen to mimic proposed clinical practice and better adapt to risk-benefit considerations. The initial active doses of 80 mg and 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 80 mg to 180 mg.

Table 3: Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	80 or 120* mg	40 or 60 mg	80 mg to 180 mg
3	80 or 120* mg	40 or 60 mg	80 mg to 180 mg
		Total Cumulative Dose	240 mg to 480 mg

* Unless tolerability issues emerge with the first dose or it is refused by the participant.

In the first Experimental Session, the initial dose will be 80 mg MDMA. In the second and third Experimental Sessions, the initial dose may be increased to 120 mg MDMA unless tolerability issues emerge with the first dose or it is refused by the participant. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the site team based on observed response, tolerability to the previously administered dose, and discussion with the participant. 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. If the participant received an initial dose of 80 mg, a 40 mg supplemental dose will be used. If the participant received an initial dose of 120 mg, a 60 mg supplemental dose will be used. If drug supply does not permit availability of 60 mg capsules, a reduced supplemental dose of 40 mg may be administered following the 120 mg initial dose.

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 teams 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 Team Qualifications

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

- One person licensed to manage and administer controlled substances for each site
- A physician to assess participant eligibility at Screening
- One or more two-person therapy pairs, male/female preferred
- One person per therapy pair is required to be licensed to provide psychotherapy according to state or province and local requirements
- If one person on the therapy team is unlicensed, they will work under the direction of the licensed team member

5.3 Training and Supervision

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 from the training team during a MAPS-sponsored protocol of MDMA-assisted psychotherapy, including this protocol. The sponsor will provide clinical supervision for new therapists completing their clinical supervision requirement in this protocol, with supervision provided at dedicated time points during treatment of their first participant. All therapy pairs participating in the trial will receive clinical supervision as requested or deemed necessary by the pair's assigned supervisor.

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 ratings will be conducted by qualified, trained, and regularly-calibrated adherence raters who will analyze video data from specific select Preparatory Sessions, Experimental Sessions, and Integrative Sessions conducted with individual participants. Adherence criteria assess adherence to overall aspects of the treatment modality, such as the creation and

nurturance of a safe therapeutic container and support of the participant's inner-directed process, as well as constructs specific to each type of session (e.g., emotional and factual preparation of the participant for Experimental sessions during the Preparatory phase; appropriate use of silence, music, touch, and trauma processing in Experimental sessions; and support of the participant's unfolding emotional, cognitive, and somatic experiences during the Integrative phases). The elements included in adherence criteria are specific to each type of session and are defined in the Adherence Manual. These ratings will be collected, at minimum, for each therapy 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 6: Time and Events-Study Measures.

Table 4: Protocol Objectives and Assessment Tools

Objectives	Measure	Measure Type
Eligibility		
Assess psychiatric disorders	MINI	Eligibility
Primary		
Assess changes in PTSD symptom severity from Visit 3 to Visit 16	PCL-5	Outcome
Secondary		
Assess changes in self-reported functional impairment from Visit 3 to Visit 16	SDS	Outcome
Safety		
Compare relative incidence of positive or serious ideation and suicidal behavior	C-SSRS	Safety
Exploratory		
Explore the effect of presence of secondary traumatic stressors during the assessment period as a covariate on the PCL-5 Total Severity analyses	LEC-5 PCL-5	Outcome
Assess changes in depression symptoms from Visit 3 to Visit 16	BDI-II	Outcome
Assess changes in chronic pain from Visit 3 to Visit 16	CPGS	Outcome
Assess changes in quality of life from Visit 3 to Visit 16	EQ-5D-5L	Outcome
Assess changes in nicotine use from Visit 3 to Visit 16	SRNU	Healthcare cost
Assess changes in eating habits from Visit 3 to Visit 16	EAT-26	Healthcare cost
Assess changes in workplace productivity from Visit 3 to Visit 16	HPQSF	Healthcare cost
Assess changes in alcohol use from Screening to Visit 16	AUDIT	Healthcare cost
Assess changes in drug use from Screening to Visit 16	DUDIT	Healthcare cost
Assess facility-based healthcare utilization at Screening	UFEC	Healthcare cost

6.1 Primary Outcome Measure

6.1.1 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 [71]. Participants indicate how much distress they have experienced in the last 2 weeks 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).

6.2 Secondary Measure

6.2.1 SDS (Sheehan Disability Scale)

The SDS is a 5-item measure of functional impairment [72]. The items indicate degree of impairment in the domains of work/school, social life, and home life, with response options based on a 10-point scale (0=not at all to 10=extremely), and five verbal tags (not at all, mildly, moderately, markedly, extremely). The SDS has high internal consistency and accurately identified 80% of a sample of primary care patients with mental disorders [73]. The Customized version of the SDS for PTSD for MAPS was developed utilizing the standard SDS. The first three items indicate degree of impairment in the domains of work/school, social life, and home life, with response options based on a 10-point scale (0=not at all to 10=extremely), and five verbal tags (not at all, mildly, moderately, markedly, extremely). The remaining two items assess Days Lost and Days Unproductive during the reporting period. The SDS for PTSD for MAPS maintains the same scale conventions as the standard SDS. To limit missing data, the summary measure used to analyze the treatment effect on SDS is the mean of the 3 item responses at each visit. Any participant who did not work during the reporting period due to reasons related to PTSD is scored as maximal work-related impairment on item 1. Any participant who did not work during the reporting period due to reasons not related to PTSD reports on the reason for not working and Item 1 is skipped. The SDS for PTSD for MAPS has been approved by the author (Dr. David Sheehan) for use in MAPS Research and is referred to throughout the protocol as SDS. The SDS for PTSD for the MAPS takes approximately 5 minutes to complete.

6.3 Safety Measures

6.3.1 C-SSRS (Columbia Suicide Severity Rating Scale)

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [74]. In this study, the Since Last Visit version will be used. The first assessment will measure suicidality since the last administration in the parent study and for the previous two weeks. All subsequent administrations will assess suicidality since the last administration in this protocol. The C-SSRS assesses suicidal ideation, ideation intensity, and behavior and consists of a series of questions and can be administered during a face-to-face interview or over the telephone. 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 [75]. The MAPS Adapted C-SSRS was developed utilizing Dr. Kelly Posner's Columbia Suicide Severity Scale. The MAPS Adapted C-SSRS maintains the content and flow of the standard C-SSRS. The scale was adapted to modify formatting and add additional administrative guidance to reduce rater and data entry errors. The MAPS Adapted C-SSRS has been approved by Dr. Posner for use in MAPS Research and is referred to throughout the protocol as C-SSRS. The MAPS Adapted C-SSRS takes approximately 10 minutes to complete.

6.4 Screening Measures

6.4.1 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 [76], is now compatible with DSM-5 and will be administered by a member of the Independent Rater (IR) 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 [77]. The MINI takes around 75 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 [77, 78] Testing on nonpsychiatric samples did not create false positives [76]. The IR pool will not assess the PTSD or Antisocial Personality Disorder modules.

6.5 Exploratory Measures

6.5.1 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 as well as presence of other life stressors. The participant indicates whether each event listed has occurred since the last administration of the measure (in parent study), permitting the possibility of marking multiple events [79].

6.5.2 BDI-II (Beck Depression Inventory II)

The BDI-II is a revision of the BDI, a 21-item self-report measure [80, 81] that will serve as a measure of depression symptom severity over the prior 2 weeks [82]. 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 [82]. 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 [82, 83]. Higher scores indicate more severe depressive symptoms.

6.5.3 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 regarding pain intensity in the past 6 months, and the response to the other item is made on a 10-point Likert scale regarding present-day pain [84]. 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 [85].

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

The EQ-5D-5L is a two-part self-report questionnaire assessing health status. It consists of five dimensions; mobility, self-care, usual activities, pain-discomfort and anxiety-depression, and one visual analog scale (VAS). Responses are made on each dimension by checking one of five statement that best reflects their health on the day of measure completion, from the healthiest or fewest problems (e.g., "I have no trouble walking about") to the most trouble (e.g., "I am unable to walk about") [86, 87]. In the second part of the EQ-5D-5L, current degree of health ("your health today") is indicated by marking a 20 cm line marked form one to 100, with 100 considered "the best health you can imagine" and one "the worst health you can imagine." The EQ-5D-5L does not sum responses but treats each response on a dimension as a scale score, and the VAS is the location of the mark in centimeters. The scale can permit comparison across groups on health profiles, and an index can be derived from matching the five-dimension scores and the VAS response with nation-specific datasets and calculator software or statistical

software syntax designed for the measure. The EQ-5D-5L began as part of the EuroQoL measure, published in 1990 [88]. The instrument has been validated in populations from eight countries. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation [89]. The EQ-5D-5L takes about 3 minutes to complete.

6.5.5 AUDIT (Alcohol Use Disorders Identification Test)

The AUDIT is a ten-item self-report test covering alcohol use habits over the past year. Respondents answer on a 5-point scale (0=Never or none, 4=Daily or greatest number) [90]. 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 [91].

6.5.6 DUDIT (Drug Use Disorders Identification Test)

The DUDIT is an 11-item measure designed to assess presence of substance use disorders within the past year [92]. 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% [92]. The English translation was developed from a Swedish-language original. Estimated time to complete is 2 to 4 minutes.

6.5.7 SRNU (Self-reported Nicotine Use)

The SRNU is a sponsor-developed measure that will assess participant's use of nicotine, including approximate frequency of use in the last month and attitudes towards quitting. The measure will take less than 3 minutes to complete.

6.5.8 EAT-26 (Eating Attitudes Test)

The EAT-26 is a 26-item self-report measure that assesses attitudes about eating and food currently and is used to assess presence of eating disorders [93]. Responses are made on a 6-point scale (1=Always to 6=Never), and gathers information on gender, age, height, and weight. The EAT-26 produces a total score and can be used to generate a "referral score." The 27th item addresses the occurrence and frequency of specific eating behaviors, such as binge eating. Estimated time to complete is 4 to 8 minutes. Items on the EAT-26 have high reliability coefficients (Cronbach alpha of 0.83 to 0.90) and has concurrent validity [94].

6.5.9 HPQSF (Health and Work Performance Absenteeism and Presenteeism Short Form)

The HPQSF is a short form of a larger measure of health and work performance that has selected items referring to absenteeism and work performance [95]. The larger measure was created by the WHO as part of the Global Burden of Disease initiative. It consists of eight questions selected from the larger Health and Work Performance Questionnaire, with one question containing five additional items. Items include questions concerning hours worked during an average week, number of whole and partial days missed during a 4-week period, and items that rate average coworker and self-work performance on a ten-point Likert scale (1=Worst performance to 10=Top performance). Hours spent in work over a 4-week period

and over the last 7 days can be used to estimate absenteeism, and the HPQSF can also score presenteeism, a measure of actual performance in relation to possible performance. Self-reports on measure appear to match employer records of presence or absence [96], and the HPQSF appears to be reliable between one time point and another (reliability of 0.52) and is sensitive to change [95].

6.5.10 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 since termination from the parent study.

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 5: Time and Events-Study Procedures

	Screening Period (1 to 6 weeks)			**Preparatory Period** (At least 5 days, depending on medication tapering)			
	Screening			**Preparatory**			
Visit	Phone Screening	Screening	IR Screening	V0	V1	V2	V3
Visit Description	Phone Calls	In-person/Remote Visits & Labs	Telemedicine	Enrollment	Prep. 1	Prep. 2	Prep. 3
Visit Timing	Prior to Initial Screening	Over 7 to 70 days	After initial screening visit	2 to 14 days post IR Screening	0 to 14 days after V0	At least 2 days after V1 (depending on tapering)	Post V2 & Taper; 1 to 14 days before V4
Initial Phone Screen	✓						
Informed Consent	Send Copy	✓					
Follow-up Phone Screen	✓						
Assess Eligibility	✓	✓	✓	✓	✓	✓	✓
Medical/Psychiatric History	✓ [A]	✓			✓	✓	✓
Past/Current Medication & Adherence	✓	✓		✓	✓	✓	✓
Weight		✓					
Resting Vitals		✓					
Physical Exam		✓					
ECG & Rhythm Strip		✓					
Clinical Lab Tests		✓					
Drug Screen		✓					✓
Pregnancy Screen		✓					✓
Enter Participant in eCRF		✓					
Independent Rater Assessment			✓				
Medication Taper				✓	✓	✓	
Study Enrollment				✓			
All AEs [B]				✓	✓	✓	✓
90-min Preparatory Session					✓	✓	✓
Phone Call Follow-up [C]						✓	
Measures (ePRO or Clinician-Administered [D]		✓	✓		✓	✓	✓

[A] At Screening, collect data on previous hospitalizations and healthcare utilization. Site physician may request participants to obtain medical/psychiatric records generated since the end of the parent study as required for eligibility assessment

[B] 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

[C] If needed, call participant to confirm medication tapering and stabilization is complete prior to Visit 3

[D] Refer to Table 6: Time and Events-Measures for details

	Treatment Period 8 to 20 weeks												
	Treatment 1				**Treatment 2**				**Treatment 3**				**Study Termi-nation**
Visit	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Visit Description	Exp. 1	Int. 1.1	Int. 1.2 [F]	Int. 1.3 [F]	Exp. 2	Int. 2.1	Int. 2.2 [F]	Int. 2.3 [F]	Exp. 3	Int. 3.1	Int. 3.2 [F]	Int. 3.3 [F]	Study Termination
Visit Timing	1 to 14 days after V3	Morning after V4	10 to 18 days after V4	At least 2 days after V6; 1 to 14 days before V8	21 to 56 days after V4	Morning after V8	10 to 18 days after V8	At least 2 days after V10; 1 to 14 days before V12	21 to 56 days after V8	Morning after V12	10 to 18 days after V12	At least two days after V14	24 to 32 days after V12
Past/Current Medication & Adherence	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Drug Screen	✓				✓				✓				
Pregnancy Screen	✓				✓				✓				✓
All AEs [A]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Container Assignment [B]	✓				✓				✓				
Administer IMP	✓				✓				✓				
At least 6-hour Exp. Session	✓				✓				✓				
BP, Pulse, Temperature	✓ [C]	✓ [H]			✓ [C]	✓ [H]			✓ [C]	✓ [H]			✓ [D]
Potential Overnight Stay	✓				✓				✓				
90-min Integrative Session		✓	✓	✓		✓	✓	✓		✓	✓	✓	
Phone Call Follow-up [E]		✓				✓				✓			
Weight													✓
Measures (ePRO or Clinician-Administered [G]	✓	✓ [E]	✓	✓	✓	✓ [E]	✓	✓	✓	✓ [E]	✓	✓	✓

[A] 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

[B] Obtain container assignment 24 to 48 hours prior to each Experimental Session

[C] During Experimental Sessions, vitals are measured within 15 minutes before Investigational Product administration, immediately before the supplemental dose is administered (or would be, if supplemental dose not given), and approximately 6 hours after initial dose, and as needed. Additional measurements to be taken if clinically indicated (e.g., if blood pressure does not return to baseline).

[D] At Study Termination, only blood pressure needs to be measured

[E] 14 days of phone call follow-up: every other day after the Experimental Session; includes C-SSRS administration and AE collection

[F] All Integrative Sessions must be at least 2 days apart

[G] Refer to Table 6: Time and Events-Measures for details

[H] If clinically indicated.

Table 6: Time and Events-Study Measures

		Screening		Preparatory Period			Treatment 1				Treatment 2				Treatment 3				Study Termination
	Visit #	Screening	IR Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Visit Description	**~Time to Complete Measure (minutes)**	Site Visit	Tele-medicine	Prep. Session 1	Prep. Session 2	Prep. Session 3	Exp. Session 1	Int. Sessions 1.1	Int. Session 1.2	Int. Session 1.3	Exp. Session 2	Int. Sessions 2.1	Int. Session 2.2	Int. Session 2.3	Exp. Session 3	Int. Sessions 3.1	Int. Session 3.2	Int. Session 3.3	Study Termi-nation
C-SSRS [A]	10	✓	✓			✓	✓[B]	✓	✓	✓	✓[B]	✓	✓	✓	✓[B]	✓	✓	✓	✓
MINI	75		✓																
LEC-5	5	✓				✓			✓				✓				✓		✓
PCL-5	8	✓				✓			✓				✓				✓		✓
SDS	5					✓													✓
BDI-II	5					✓													✓
CPGS	5					✓													✓
EQ-5D-5L	3					✓													✓
AUDIT	3	✓																	✓
DUDIT	3	✓																	✓
SRNU	3					✓													✓
EAT-26	6					✓													✓
HPQSF	5					✓													✓
UFEC	3	✓																	
~Total Time of Completing Measures (minutes)	**139**	**29**	**85**	**0** [C]	**0** [C]	**55**	**90** [B]	**10**	**23**	**10**	**90** [B]	**10**	**23**	**10**	**90** [B]	**10**	**23**	**10**	**61**

[A] All C-SSRS are Since Last Visit. The first assessment will measure suicidality since the last administration in the parent study and the last two weeks. All subsequent administrations will assess suicidality since the last administration in this protocol.
[B] Conducted pre- and post-Investigational Product administration, and every other day for 14 days after Experimental Sessions.
[C] No planned measures to be assessed at Visit 1 or Visit 2

7.1 Screening Period

7.1.1 Screening

Participants will be identified and invited to screen based on participation in a parent Phase 3 study. Prospective participants will be pre-screened by telephone according to an Institutional Review Board (IRB)-approved script to ascertain if they meet basic eligibility criteria. All individuals who are pre-screened should be recorded on the Screening Log using their Participant Number from the parent study. 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 the site for in-person 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) or the treating therapist or psychiatrist to confirm eligibility.

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 (wet-ink or electronic) 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, within 6 weeks of signing of the ICF. All procedures must be completed but there can be some flexibility in timing and order of individual assessments. The sponsor suggests the following order of assessments to minimize in-person screening in light of COVID-19:

- Initial Eligibility, including measures, in-person discussions, and review of medical records (as needed)
- Medical Assessments, including labs, electrocardiogram (ECG), and physical exam
- Independent Rater screening

7.1.2 Initial Eligibility Assessment

Qualified site staff will:

- Collect demographics information
- Administer the Interim (Since Last Visit) C-SSRS to assess history of suicidal behavior and ideation. The first assessment will measure suicidality since the last administration in the parent study and within the last 2 weeks.

- Direct participant to complete self-reported Screening measures:
  - AUDIT
  - DUDIT
  - UFEC
  - LEC-5
  - PCL-5, under the direction of the therapy pair, who will remind them of the index trauma identified in the parent study to which PTSD symptoms should be anchored.
- Review results of all measures and discussions against eligibility criteria to assess initial eligibility. If deemed initially eligible, continue collection of information on source records, including interim and current psychotherapy, and schedule a meeting with a site physician.

7.1.3 Medical Assessments

A site physician will meet with the participant over telemedicine, the phone, or in-person to perform the following assessments:

- Collect data on hospitalizations and healthcare utilization.
- Review interim medical and psychiatric history with the participant via interview.
- 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.

The site physician may deem it appropriate to collect medical and/or psychiatric records depending on the participant's medical history. Records may be requested to confirm information required for eligibility assessment or supplement a participant who does not have adequate recall of the period of time since the parent study. Records are not necessary to collect and review in all instances, but all records collected should be reviewed.

If the physician deems the participant initially eligible based on these discussions and review of medical records (as needed), the site will make an assessment about the next step for screening (either IR screening (Section 7.1.4 Independent Rater Screening) or in-person medical assessments. The sponsor suggests completing the IR Screening while the medical assessments are being scheduled.

In-Person Medical Assessments

The physical exam must be performed by a qualified physician, and lab assessments must be completed at a designated lab. Some or all of these assessments may be at outside facilities. Medical assessments will include:

- Perform urine pregnancy test for participants who are able to become pregnant.
- Perform a urine drug test.
- Collect blood pressure, pulse, and body temperature measurement.
- Measure 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 to 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 a condition such as controlled hypertension or Diabetes Mellitus (Type 2) that warrants additional testing to ensure they do not have evidence of significant vascular or other cardiac disease, they have no other evidence of significant 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 stress 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 (as requested), 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 C-SSRS to the IR. Although the IR visit is by telemedicine, the participant will be provided a location to complete the telemedicine visits at the study site if needed. The site can provide technical support before the assessment and therapeutic support after, if needed. For all IR visits, the site team will confirm with the participant that they should have adequate internet access and be in a private and quiet space where they are comfortable talking about personal matters.

7.1.4 Independent Rater Screening

An IR will continue the eligibility assessment via telemedicine after reviewing the results of the LEC-5 and most recent C-SSRS. The IR interview may be recorded to assess reliability of ratings. If possible, the potential participant should be present at the study site during this assessment, in case the therapy pair is needed for support. The IR will perform a C-SSRS and contact the therapy pair after the call to present any concerns. The therapy pair will follow-up with the participant to ensure safety, provide support, recommend treatment, or schedule a visit to the study site. The IR will complete MINI interview to assess psychiatric disorders, skipping the modules for PTSD and Antisocial Personality Disorder.

The results from the MINI 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 site staff deem the participant eligible, schedule Enrollment (Visit 0).

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 assessment. The Senior IR 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 or interview, but the investigator believes the participant presents with a particular disorder, they may diagnose and deem the participant ineligible if appropriate.

7.1.5 Enrollment

In advance of Visit 0, the site team will review all notes from Screening visits, medical assessments, IR assessments, notes, discussions, medical records (as requested), and measures against eligibility criteria. 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 at each site, if a potential participant is eligible, the study team will contact the Medical Monitor and send a request for enrollment, including medical history, for approval to enroll the potential participant. If a participant is approved by the sponsor, the participant will be notified of enrollment at Visit 0 in-person, via telemedicine, or by telephone. A medication tapering plan will be discussed with the participant, if applicable. 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 30 days after Independent Rater Screening is completed. Visit 0 and Visit 1 may take place on the same day.

7.2 Preparatory Period

Participants will undergo three Preparatory Sessions (Visits 1, 2, and 3) lasting approximately 90 minutes with the therapy pair prior to the first Experimental Session. 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 promoting a safe set and setting for confronting trauma-related memories, emotions, and thoughts in preparation for MDMA-assisted therapy.

Telephone calls may be scheduled between visits if indicated for tapering, safety, or any further questions about medical history. Each session may be recorded. With awareness of the therapy team, CI, and Medical Monitors, one or more Preparatory Sessions may be performed via telemedicine.

The Preparatory Period will be initiated 0 to 14 days after Visit 0. The duration of the preparatory period will be at a minimum 5 days but can be as long as needed depending on duration of medication tapering. There must be at least 48 hours between Preparatory Sessions.

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-Treatment Early Termination, notify the potential participant that they are unfortunately not eligible for the study, and not schedule additional assessments.

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

- 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.
- Confirm that medication tapering is ongoing or complete, as appropriate.
- Discuss goals and expectations for the Experimental Session, following standard procedures and techniques described in the Treatment Manual [97].
- At Visit 4, administer the Since Last Visit C-SSRS.

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.

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.

7.2.1 Preparatory Sessions 1 and 2

Preparatory Session 1 (Visit 1) will occur 0 to 14 days after Visit 0. The visit timing should take in to account appropriate times for monitoring medication tapering.

Preparatory Session 2 (Visit 2) will occur 2 to 75 days after Visit 1. The visit timing should take into account appropriate times for monitoring medication tapering.

If tapering is ongoing at Preparatory Session 2 (Visit 2), the site team will schedule a telephone phone call within 7 days of completion of tapering and stabilization. If tapering is complete or not needed, the site team will confirm eligibility and schedule Preparatory Session 3 (Visit 3) as soon as possible.

7.2.2 Preparatory Session 3

Preparatory Session 3 (Visit 3) should take place as soon as possible after medication tapering and stabilization and 1 to 14 days prior to Experimental Session 1 (Visit 4).

The site team will confirm eligibility and ensure that the participant continues to agree to all lifestyle modifications. If any requirements are not met before or during Visit 3, the participant will be considered a Pre-Treatment Early Termination.

For eligible participants, qualified site staff will:

- Perform urine pregnancy test for participants who are able to become pregnant.
- Perform urine drug test.
- Administer Since Last Visit C-SSRS to determine suicidal risk.
- Actively support participant in the completion of Baseline self-reported measures. Completion of measures does not need to be recorded.
    - PCL-5, under the direction of the therapy pair, who will remind them of the index trauma identified in the parent study to which PTSD symptoms should be anchored

  - LEC-5
  - SDS
  - BDI-II
  - CPGS
  - EQ-5D-5L
  - SRNU
  - EAT-26
  - HPQSF
- Complete the third 90-minute Preparatory Session with the purpose of confirming all enrollment eligibility is met and completing final preparation for the first Experimental Session.
- 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.

7.3 Treatment Period

During the Treatment Period, which occurs over a duration of 8 to 20 weeks, participants will complete three Experimental Sessions, followed by Integrative Sessions. Each treatment consists of an Experimental Session, followed the morning after by an Integrative Session, phone follow-ups over the next 14 days, and two additional Integrative Sessions. The Experimental Sessions will be scheduled 3 to 8 weeks apart. The PCL-5 will be assessed at three visits during the Treatment Period: Integrative Session 1.2 (Visit 6), Integrative Session 2.2 (Visit 10), and Integrative Session 3.2 (Visit 14). The Primary Outcome PCL-5 will be assessed at Study Termination (Visit 16).

7.3.1 Experimental Sessions

There will be three open-label Experimental Sessions (Visits 4, 8, 12). Procedures for MDMA-assisted therapy will remain the same across all sessions and all procedures regardless of dose received. Experimental Sessions must be at least 6 hours long, measured from 30 minutes prior to IMP administration. The Experimental Sessions will consist of:

- Experimental Session 1 (Visit 4) will occur 1 to 14 days after Preparatory Session 3 (Visit 3). The first Experimental Session will include 80 mg of MDMA followed by a supplemental half-dose 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 8) will occur 21 to 56 days after Experimental Session 1 (Visit 4) and 1 to 14 days after Integrative Session 1.3 (Visit 7). A dose of 80 or 120 mg MDMA will be administered. A supplemental dose (40 mg or 60 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. If the participant received an initial dose of 80 mg, a 40 mg supplemental dose will be used. If the participant received an initial dose of 120 mg, a 60 mg supplemental dose will be used. If drug supply does not permit availability of 60 mg capsules, a reduced supplemental dose of 40 mg may be administered following the 120 mg initial dose.
- Experimental Session 3 (Visit 12) will occur 21 to 56 days after the second Experimental Session (Visit 8) and 1 to 14 days after Integrative Session 2.3 (Visit 11). A dose of 80 or 120 mg MDMA will be administered. A supplemental dose (40 mg or 60 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. If the participant received an initial dose of 80 mg, a 40 mg supplemental dose will be used. If the participant received an initial dose of 120 mg, a 60 mg supplemental dose will be used. If drug supply does not permit availability of 60 mg capsules, a reduced supplemental dose of 40 mg may be administered following the 120 mg initial dose.

Table 7: Schedule of Procedures for Experimental Sessions

Approximate Time during an 8 hour session	Procedure or Action
9:30	Urine drug screen and pregnancy test, concomitant medication information collected, participant acclimated to environment, C-SSRS. Begin video recording.
9:55	Baseline BP, body temperature, pulse
10:00	**IMP Administration**
11:30	BP, body temperature, pulse **Supplemental Dose Administration**, unless tolerability issues emerge with the first dose, or it is refused by the participant.
17:30	C-SSRS, BP, body temperature, pulse

Pre-IMP administration

In the hours before IMP administration, the following procedures will take place:

- 24 to 48 hours prior to each Experimental Session, the site team will obtain the container assignment.
- On the day of the Experimental Session, the participant will arrive approximately 30 to 60 minutes prior to IMP administration.
- The site team will ensure the participant has not used caffeine or nicotine 2 hours prior and has fasted and not used cannabis or alcohol since 12:00 AM (midnight) 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 test that has been confirmed is cause for withdrawal from the protocol.
- The therapy pair will administer Since Last Visit C-SSRS.
- 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. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the therapy pair in consultation with the site physician based on observed response, tolerability to the previously administered dose, and discussion with the participant.
- 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 (initial dose will be administered within 15 minutes of baseline blood pressure, body temperature, and pulse).

During the Experimental Session

- At approximately 10:00 A.M., 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.
- 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 administer Since Last Visit C-SSRS.
- The therapy pair will record AEs and concomitant medications.
- 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.
- Participants with persistent elevations in blood pressure at the end of Experimental Sessions will have additional blood pressure assessments after the session and the next morning during the integration session. If deemed necessary, the blood pressure will be monitored until the pressure returns to baseline or an acceptable pressure is reported as determined by the study physician. Any changes in antihypertensive therapy will be recorded on the Concomitant Medication log and the event will be reported on the Adverse Event eCRF.
- The therapy pair or site physician shall remain available to participants via 24-hour cellular phone for integration, as needed.

At the end of each Experimental Session, the therapy pair (in consultation with site physician, if necessary) will assess the participant to decide if they are physically and emotionally stable. If the participant is not stable, the therapy pair and/or site physician will stay with the participant until stable or escalate for further care as appropriate.

Overnight Stay

If a participant is deemed medically and psychologically stable by the therapy pair at the end of the Experimental Session, the session will be ended and participant care transferred to the Night Attendant.

If a participant is deemed to be not psychologically stable at the end of the Experimental Session, they will remain under the care of their therapy pair. The therapy pair will continue to evaluate the participant to make further disposition recommendations depending on the participant's psychological condition. This could include: continued observation, psychological support and/or psychopharmacologic interventions; or further evaluation for potential transfer as appropriate per site Standard Operating Procedures (SOPs).

The following procedures will take place at overnight stays:

- 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 for 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 the day after the Experimental Session, 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. The therapy pair will follow-up with the participant by telephone every other day for 14 days after each Experimental Session. If an Integrative Session falls on the date of a planned phone call, the phone call does not need to be performed. Each call will last on average 5 to 20 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 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.
- Administer the Since Last Visit C-SSRS.
- Inquire about concomitant medication use and adherence.
- Offer support in accordance with the Treatment Manual.

7.3.3 Integrative Sessions

After each Experimental Session, three Integrative Sessions will take place. Each session will consist of 90 minutes of therapy. Integrative Sessions should not be less than 48 hours apart. The therapy pair may record the sessions. Integrative Sessions 1.2, 1.3, 2.2, 2.3, 3.2, and 3.3 may be performed via telemedicine.

Treatment 1

- Integrative Session 1.1 (Visit 5): morning after Experimental Session 1 (Visit 4).
- Integrative Session 1.2 (Visit 6): 10 to 18 days after Experimental Session 1 (Visit 4). The participant will complete the PCL-5 and LEC-5.
- Integrative Session 1.3 (Visit 7): at least 2 days after Integrative Session 1.2 (Visit 6) and 1 to 14 days in advance of Experimental Session 2 (Visit 8). This visit serves two purposes: to continue integration and to prepare for the next Experimental Session.

Treatment 2

- Integrative Session 2.1 (Visit 9): morning after Experimental Session 2 (Visit 8).
- Integrative Session 2.2 (Visit 10): 10 to 18 days after Experimental Session 2 (Visit 8). The participant will complete the PCL-5 and LEC-5.
- Integrative Session 2.3 (Visit 11): at least 2 days after Integrative Session 2.2 (Visit 10) and 1 to 14 days in advance of Experimental Session 3 (Visit 12). This visit serves two purposes: to continue integration and to prepare for the next Experimental Session.

Treatment 3

- Integrative Session 3.1 (Visit 13): morning after Experimental Session 3 (Visit 12).
- Integrative Session 3.2 (Visit 14): 10 to 18 days after Experimental Session 3 (Visit 12). The participant will complete the PCL-5 and LEC-5.
- Integrative Session 3.3 (Visit 15): at least 2 days after Integrative Session 3.2 (Visit 14).

During Integrative Sessions, 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. Record AEs as described in Section 10.0 Safety.
- Inquire about concomitant medication use and adherence.
- Administer Since Last Visit C-SSRS to determine suicidal risk.
- 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 pair 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 pair will be supportive, validate the experience, and facilitate understanding and emotional clearing.
- Be accessible for additional support via phone or telemedicine if needed.
- At each second Integrative Session, participants will complete the LEC-5 and PCL-5, under the direction of the therapy pair, who will remind them of the index trauma listed in the parent study to which PTSD symptoms should be anchored.

7.4 Study Termination

Study Termination (Visit 16) will take place 24 to 32 days after the Experimental Session 3 (Visit 12) and after the last Integrative Session 3.3 (Visit 15). 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.
- Administer Since Last Visit C-SSRS.
- Measure weight (used to calculate BMI).
- Measure blood pressure.
- Perform urine pregnancy test for participants who are able to become pregnant.
- Provide and discuss a study Exit Plan/Plan for Moving Forward.
- Ask them to enroll into the LTFU extension study with a visit at least 6 months after the last Experimental Session. Review contact information and Informed Consent procedures for LTFU.
- Actively support participant in completion of Study Termination self-reported measures. Completion of the measures does not need to be recorded.
    - LEC-5
    - PCL-5, under the direction of the therapy pair, who will remind them of the index trauma listed in the parent study to which PTSD symptoms should be anchored
    - SDS
    - BDI-II
    - CPGS
    - EQ-5D-5L
    - AUDIT
    - DUDIT
    - SRNU
    - EAT-26
    - HPQSF

After all Study Termination measures and assessments are completed, the participant is considered terminated from the study. The participant can resume normal everyday life.

7.4.1 Extension Studies

Upon completion of the study, defined as completing at least one Experimental Session and one PCL-5 assessment beyond Baseline and terminating participation, participants will be asked to join the LTFU extension study to observe long-term effects. This study will not involve any additional Experimental Sessions or administration of IMP. The ICF for this study will be provided to eligible participants at the Study Termination visit if available. This study will measure outcomes at least 6 months after the last Experimental Session.

Any sub-studies will be detailed in separate documents.

7.4.2 Exit Plan/Plan for Moving Forward

At Study Termination, participants will be provided with an Exit Plan/Plan for Moving Forward. This Exit Plan/Plan for Moving Forward 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 an Exit Plan/Plan for Moving Forward at their last contact. Screen Failures will be provided a referral if requested.

8.0 Investigational Product

8.1 Description of Active Compounds

The Active Pharmaceutical Ingredient (API) to be used in this protocol is MDMA (as hydrochloride salt [HCl]). 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 IMP. The IMP will be compounded with inactive excipients such as mannitol and magnesium stearate.

Table 8: Study Medication Intervention(s) Administered

Intervention Label	**Active Intervention**
Intervention Name	3,4-methylenedioxymethamphetamine (MDMA) as a hydrochloride salt (HCl)
Intervention Description	Initial doses (per Experimental Session) include 80 mg or 120 mg MDMA HCl, followed 1.5 to 2 hours later by a supplemental dose of 40 mg or 60 mg MDMA HCl.
Type	Drug
Dose Formulation	hydroxypropylmethylcellulose (HPMC) capsule
Unit Dose Strength(s)	40 mg or 60 mg MDMA HCl
Dosage Level(s)	Initial dose: 80 mg MDMA HCl for first session and 80 mg or 120 mg MDMA HCl for following sessions Supplemental dose: 40 mg or 60 mg MDMA HCl
Inactive Ingredients	Mannitol and magnesium stearate
Route of Administration	Oral
Use	Experimental
IMP and NIMP/AxMP.	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in an open-label container. Each container will be labeled as required per country and federal, state, and local regulations. This will include the following: *Caution: New Drug – Limited by Federal (or United States) law to investigational use.*

8.1.1 Doses

This study will explore the effectiveness of three Experimental Sessions of therapy assisted by flexible doses of MDMA. Initial doses per Experimental Session include 80 mg or 120 mg MDMA HCl compounded with mannitol and magnesium stearate, followed 1.5 to 2 hours later by a supplemental dose (40 mg or 60 mg MDMA HCl). If the participant received an initial dose of 80 mg, a 40 mg supplemental dose will be used. If the participant received an initial dose of 120 mg, a 60 mg supplemental dose will be used. If drug supply does not permit availability of 60 mg capsules, a reduced supplemental dose of 40 mg may be administered following the 120 mg initial dose. Total amounts of MDMA HCl to be

administered per Experimental Session range from 80 mg to 180 mg. All drug is encapsulated with hydroxypropyl methylcellulose (HPMC) capsules.

Refer to Table 3: Dose Regimen of MDMA.

8.1.2 Dose Modifications

A participant will receive a divided-dose of 120 mg or 180 mg per Experimental Session. In the first Experimental Session, the initial dose will be 80 mg MDMA HCl. In the second and third Experimental Sessions, the initial dose may be increased to 120 mg MDMA HCl unless tolerability issues emerge with the first dose or it is refused by the participant. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the therapy pair the in consultation with the site physician based on observed response, tolerability to the previously administered dose, and discussion with the participant. 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. If an AE requiring medical attention occurs between the initial and supplemental dose this will be evaluated as a potential tolerability issue by the site physician. If a participant prefers not to take the supplemental dose, the reason will be documented. If the participant received an initial dose of 80 mg, a 40 mg supplemental dose will be used. If the participant received an initial dose of 120 mg, a 60 mg supplemental dose will be used. If drug supply does not permit availability of 60 mg capsules, a reduced supplemental dose of 40 mg may be administered following the 120 mg initial dose.

8.1.3 Stability

IMP will be manufactured and packaged according to current Good Manufacturing Practices (cGMP). Six-month accelerated stability studies will be completed for the IMP along with an ambient stability study that will continue throughout the duration of the study. 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 each study site. Each dose of MDMA may be dispensed by the Schedule I license holder (or equivalent) or designee. Additional doses of MDMA that are not administered to a participant, will be kept in the open-label containers for administration in future sessions or to other participants.

All labels will comply with local, state/provincial, and national regulations. Each package will be labeled with a unique container number, protocol number, IMP name, lot number, sponsor name and contact information, dosage form, route, directions for administration, and storage conditions. A statement that the IMP is restricted to clinical trial use only will be included on each package.

8.2.2 Accountability

Forms will be provided to track IMP accountability and administration throughout the study. IMP accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all local, state, and federal regulations and forms pertaining to the use of controlled substances, and required forms will be maintained by the appropriate controlled substance license holder or delegate.

Each container label will contain a unique container number. The container numbers will be used to track IMP administration in the Source Record and the IMP administration log.

8.2.3 Storage

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

8.2.4 Administration

IMP will only be removed for a single Experimental Session at a time and 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 tolerability issues emerge with the first dose or it is refused by the participant. Each dose (initial and supplemental) will be administered with a glass of electrolyte-containing fluid.

A person at the site authorized to manage and administer controlled substances will dispense the appropriate IMP for each Experimental Session. If a supplemental dose is not administered, the unused IMP will be retained securely.

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

Every participant will be tracked using the same participant number used in the parent study.

8.4 Bias Minimization

Eligibility will be determined by review of screening by the PI, site team and as needed the sponsor Medical Monitor prior to enrollment confirmation. Participants, site staff, and the sponsor will be aware that each participant in MAPPUSX will be receiving open-label MDMA.

To ensure that all participants 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 hours long. The sponsor will monitor data in real-time to ensure complete data collection for all participants, including those who discontinue treatment. Sites will be required to make and document a specific number of attempts to obtain follow-up data per protocol. All participants who receive at least one dose of IMP and complete at least one follow-up assessment will be included in the final mITT primary effectiveness analysis.

9.0 Risks

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of MDMA may be found in the IB and Informed Consent Form (ICF).

9.1 Risk Assessment

Potential risks, summaries, rationale, and mitigation strategy can be found in Table 9: Risk Assessments.

Table 9: Risk Assessments

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk of IMP		
Cardiovascular and Cerebrovascular Events	MDMA transiently increases heart rate and blood pressure in a dose-dependent manner that is generally not clinically concerning for physically healthy individuals. These changes typically last no more than 6 hours. Most people do not experience elevations in cardiovascular parameters that exceed those seen after moderate exercise. An examination of safety data drawn from Phase 2 and Phase 3 studies of MDMA-assisted therapy detected a dose-dependent increase in systolic BP and to a lesser extent diastolic BP. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing. MDMA is not likely to increase risk of QTc interval prolongation based on a definitive hERG study and had no effect on qualitative or quantitative ECG parameters in an *in vivo* dog cardiovascular study, see IB.	• Participants with documented significant cardiovascular risk factors, including uncontrolled hypertension will be excluded, see Section 3.2 Exclusion Criteria. • ECG and a 1-minute rhythm strip will be completed at screening to assess for undiagnosed cardiac conduction abnormalities. • Participants with controlled hypertension or other cardiac risk factors (e.g., diabetes mellitus) will undergo a cardiovascular evaluation and risk mitigation per the local standard of care to assess cardiac function and risk of cerebrovascular events. • Before and after IMP administration in Experimental Sessions, the therapy teams monitor vital signs. The therapy team should attend to clinical signs and symptoms of potential rare complications of the cardiovascular effects of MDMA, such as stroke or acute myocardial infarction during Experimental Sessions. In the unlikely event any such situation arise, study teams will seek immediate emergency medical attention. • Participants with persistent elevations in blood pressure at the end of Experimental Sessions will have additional blood pressure assessments after the session and the next morning during the integration session. If deemed necessary the blood pressure will be monitored until the pressure returns to baseline or an acceptable pressure is reported as determined by the study physician. Any changes in antihypertensive therapy will be recorded on the concomitant medication log and the event will be reported on the adverse event eCRF.
Negative Psychological Impact	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 integrating their experience after the MDMA effect has subsided.	• MDMA is only administered as an adjunct to supportive psychotherapy. • Non-drug preparatory sessions will be conducted before experimental sessions. • Three non-drug integrative sessions will be conducted after each experimental session. • Participants who may be more vulnerable to destabilizing reactions (such as people diagnosed with bipolar affective disorder Type 1 or psychotic disorders) will be excluded. • Phone contact with participants will be arranged during the week following the Experimental Sessions. • An escort to and from the clinical site following each experimental session is required.

Thermoregulatory Events	In MAPS-sponsored Phase 2 and Phase 3 studies, MDMA administered in a controlled setting can produce a slight increase in body temperature (up to approximately 1° C).	• Participants with a known history of drug-induced hyperthermia will be excluded. • During experimental sessions, ambient temperature should be kept at a comfortable level. If a participant's temperature rises more than 1° C or the participant states that they feel hot, attempts should be made to decrease body temperature and increase comfort by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the participant. • If body temperature rises more than 1.5° C above baseline despite these efforts, the site clinician should be consulted.
Osmolarity Changes	MDMA causes AVP release, which can cause changes in osmolality under certain circumstances.	• Participants with a recent history of clinically significant hyponatremia will be excluded. • Serum electrolytes are assessed during screening, and participants with clinically significant hyponatremia will be excluded. • Participants will be limited to a maximum of 3 liters of fluid consumption during experimental sessions.
Reproductive and Developmental Risks	MDMA has been demonstrated to be negative for genotoxicity, both *in vitro* and *in vivo*, with and without metabolic activation. While there are no clinical data on the use of MDMA in pregnant individuals, repeated dose toxicity studies of adequate duration, fertility, early embryonic development, and embryofetal development studies of MDMA in rats and rabbits have not found direct or indirect harmful effects with respect to reproductive toxicity, see IB.	• Participants who are pregnant will be excluded from participation. • Urine pregnancy tests will be conducted during screening and immediately prior to any experimental session. Any positive urine pregnancy test may be followed by a confirmatory serum analysis. • A final urine pregnancy test will be conducted after the end of systemic exposure. • Participants who are able to become pregnant will be required to adhere to contraceptive measures with a <1% failure rate, as described in Section 10.3.2 Contraception Guidelines. • Information on all pregnancies in participants and their partners will be collected after the start of study intervention and until the participant's final visit. Pregnancies will be followed until the outcome of the pregnancy is known. Live births will be followed for 30 days after delivery.
Abuse Potential	Because the medication is considered a controlled substance in the U.S. with known abuse potential, the FDA has requested that patients are consistently monitored for adverse events that could be suggestive of abuse potential among research participants treated with MDMA.	• Participants with current severe alcohol and/or substance use disorders which could pose a safety concern or interfere with the therapeutic process will not be eligible for the study, see Section 3.2 Exclusion Criteria. • MDMA is only administered under the supervision of the clinical investigator and no take-home doses are administered. MDMA administration and handling follows all regulations pertaining to the use of controlled substances within research studies. • Use of alcohol and other recreational drugs will be monitored in the study. • Behavior suggestive of abuse potential will be recorded as an AESI and reported in the same manner as an SAE, refer to Section 10.1.3 Adverse Events of Special Interest (AESI).

Risk of Other Study Procedures		
Discomfort with Medical Assessments	Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Medical examinations and blood sampling are required to establish eligibility for the study and cannot be omitted from the protocol.	• Medical examinations and blood sampling will be completed by staff with appropriate training and expertise. • Investigators will be trained to counsel participants on their laboratory findings.
Loss of privacy due to video recording of sessions	Many of the visits with participants are required to be video recorded to ensure reliability between IR assessments and adherence to the Treatment Manual. Video recordings also enable clinical supervision of site therapists. Should these recordings be accessed by unauthorized individuals, there is a risk of loss of privacy. Should the participant provide information to the sponsor either directly, or through one of the sponsor's electronic systems, and against recommended process, this may result in unintended identification of the participant. Because of the nature of the study (providing therapy) and need for supervision and adherence rating, there is no way to conceal the participant's name, physical appearance, voice, or personal health information relating to life events and trauma history.	Video procedures are designed to meet privacy, data protection, and security standards that constitute best practices expected of facilities providing medical care and to comply with legal requirements. MAPS PBC contracts with service providers (Processors) through Data Processing Agreements to carry out personal data processing activities in accordance with US privacy laws. MAPS PBC conducts periodic data privacy impact assessments and audits to mitigate the risk of loss of privacy. Participants may ask to stop the recording at any time, and therapists will ask for participant permission to resume recording when the participant signals they are ready.

Discomfort related to therapy	During both non-drug and MDMA-assisted therapy sessions, participants are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with therapy, the discomfort associated with therapy is unavoidable and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.	• Therapy teams support participants as they bring conscious awareness to difficult feelings, memories, or body sensations during the course of treatment. This is supported through empathic presence and establishment of a strong therapeutic alliance, a safe container, and a comfortable setting in which the therapeutic process takes place. • Therapy teams may also support participants through discomfort related to therapeutic processing of trauma through a variety of practices including, but not limited to, use of music, breathwork, and sensorimotor and somatic psychotherapy practices. • Therapy teams assess participants' support networks and help participants to consider ways in which their support system can be of help during the time between therapy sessions. • During MDMA-assisted therapy sessions, MDMA may catalyze therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences without being overwhelmed by anxiety or other painful emotions. Frequently, participants are able to experience and express fear, anger, and grief as part of the therapeutic process with less likelihood of either feeling overwhelmed by these emotions or of avoiding them by dissociation or emotional numbing. • At times, a participant may experience strong "negative" emotional reactions, including feelings of loss of control. When the therapists see that the participant's distress is interfering with their ability to stay focused on the inner experience, they intervene, encouraging the participant to stay present with deeper levels of emotion, including distressing feelings, and to trust that it is safe to face the experience. The empathic presence of the therapy team can support a participant to tolerate and titrate the discomfort of addressing challenging emotions and memories in service of healing.

Tapering off psychiatric medications may result in increase in severity of underlying psychiatric symptoms or other adverse events	Previously published data indicated some psychiatric medications may blunt the effects of MDMA-assisted therapy. Therefore, ongoing psychiatric medications must be tapered and stopped at least five half-lives of parent drug or active metabolite (whichever is longer) prior to Visit 3. For non-selective irreversible MAOIs, a 2-week washout period following the taper is required (3 weeks in the case of imipramine and clomipramine, tricyclic antidepressants with MAOI activity) prior to the Visit 3. The tapering and withdrawal of such medications can lead to new or a return of symptoms these medications were initially prescribed to treat and has been known to induce suicidal ideation or behavior in some people.	• Participants will be informed of the potential risks associated with medication taper and cessation, and will be encouraged to discuss this with the prescribing clinician. • Study clinicians are encouraged to contact the prescribing clinician (with participant consent) and discuss the tapering plan. • Participants will be closely monitored during the medication tapering and AEs will be recorded. • Should a participant be unable to successfully taper off any prohibited medication, the participant will be withdrawn from the study and referred back to the prescribing clinician for evaluation and possible restart of psychiatric medication. • Participants are informed at screening that they should not initiate tapering themselves or with their prescribing clinician for study participation to ensure that the tapering plan is monitored by the site clinician and Medical Monitor.

Other		
Suicide and Risk of Self-Harm	Suicidal ideation and behavior are disease related events with high incidence in populations of people with PTSD, especially those suffering from chronic PTSD. Due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event in order to reprocess the memory in a new, therapeutic way, thoughts of ending one's life may surface during the process. In previous MAPS-sponsored clinical trials C-SSRS scores have escalated during the Preparatory Sessions, which is thought to be a result of preparatory discussion of traumatic experiences, and/or participants concomitant tapering off long-prescribed medications, such as SSRIs and benzodiazepines. During both non-drug and MDMA-assisted therapy sessions, participants are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. Participants are also asked to report on their suicidality in these sessions and follow-up phone calls through C-SSRS administration. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with therapy, the distress associated with therapy is unavoidable and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.	• Therapy teams minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with current, severe suicidal ideation or a suicide attempt within the past six months are excluded from the trial, see Section 3.2 Exclusion Criteria. However, participants with a history of suicide attempts are not excluded unless significant risk of suicidal behavior is present at the time of Screening, as this would result in enrolling a non-representative sample of the population. • If positive serious ideation or behavior occurred after study enrollment, the investigators are to make additional follow-up C-SSRS observations to ensure participant safety and to track scores until they returned to non-serious levels. • Should a participant be at serious risk to themselves, then the therapy team and site staff will intervene appropriately, consistent with professional practice standards. In extreme circumstances, this may involve summoning external crisis management teams for further assessment which may lead to involuntary hospitalization. • Attempted suicide or adverse event associated with an increase in suicidal ideation to a 4 or 5 on the C-SSRS will be reported as an AESI by the PI within 24 hours of discovery and will be followed until the outcome of the event(s) is known, refer to Section 10.1.3 Adverse Events of Special Interest (AESI).

10.0 Safety

10.1 Adverse Events, Serious Adverse Events, Adverse Events of Special Interest and Other Safety Reporting

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The collection period of AEs is from the time of signed ICF until the completion of the study termination visit (+/- 2 days). Medical occurrences that begin before the start of Visit 0, but after obtaining informed consent may be recorded as medical history or a current medical conditions, unless the event occurs as a result of a study requirement in which case the event would be reported as an AE. All AEs should be recorded regardless of the cause of the event, whether the event is deemed positive, negative or neutral by the investigator, reporter or qualified designee. The investigator will elicit information through non-leading open-ended questioning and examination of the participant about the occurrence of the AE. For each event, the following information will be recorded in the participant's record and transcribed into the AE section of the eCRF and SAE form when appropriate according to the instructions below:

- Classification of the event: serious or non-serious
- Classification of the event as an adverse event of special interest (AESI)
- Description of signs and/or symptoms. Whenever possible, the specific diagnosis for the event will be recorded. If a diagnosis cannot be made, each sign or symptom will be recorded separately (e.g., nausea and vomiting would be recorded as two separate events).
- Severity of event: mild, moderate or severe
- Relationship to study medication: related or not related
- Action taken with study medication: dose maintained, dose not changed, dose reduced, interruption of dose, drug withdrawn/discontinued, unknown, or not applicable
- Adverse event outcome: resolved without sequelae, resolved with sequelae (describe sequelae), resolving, not resolved, fatal, or unknown (lost to follow-up)
- Event onset date. If a laboratory event is reported as an AE, record the start date as the date of collection of the first lab sample that shows the change.
- Event stop date: date the event resolved

10.1.1 AE Definition

An AE is any untoward medical occurrence in a clinical study participant which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable unintended sign, including an abnormal laboratory symptom or disease temporally associated with the use of IMP, whether or not related to the IMP.

Note: For the purpose of this study, an adverse event will be considered any event that occurs within the study, whether deemed positive, negative, or neutral by the investigator, qualified designee or reporter. Examples of positive or neutral events may include, but are not limited to:

- Positive mood, calmness, talkative, elevated mood, dizziness, feeling abnormal, feeling drunk, feeling of relaxation, thinking abnormal, inappropriate affect, somnolence, mood disorders and disturbances, confusion and disorientation.

The investigator or qualified designee should carefully record any AE that occurs. Whenever possible, a diagnosis rather than a list of signs and symptoms is preferred. Treatment or intervention of an AE should not be reported as an event. The event necessitating the treatment or intervention should be reported. AEs should be followed until the events have subsided, returned to baseline or in case of permanent impairment, until the condition stabilizes.

10.1.1.1 AE Severity Grading Criteria

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

- **Mild**: No limitation in normal daily activity. Minor event requiring no specific medical intervention, asymptomatic laboratory findings only, marginal clinical relevance.
- **Moderate**: Some limitation in normal daily activity. Minimal intervention, local intervention, non-invasive intervention, transfusion, elective interventional radiological procedure, therapeutic endoscopy or operation.
- **Severe**: Unable to perform normal daily activity. Significant symptoms, which may require hospitalization or invasive intervention, elective interventional radiological procedure, therapeutic endoscopy or operation, life threatening or disabling events, events resulting in death.

Note: The terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event. The event itself may be of relatively minor medical significance (e.g., severe headache). A severe headache does not necessarily need to be considered serious unless it meets the criteria of a serious adverse event.

10.1.1.2 AE Causality Assessment

The investigator will assess the relationship between the AE and the study treatment or the study procedure using a binary causality assessment. Causality will be reported separately for each study treatment received by the participant.

- **Related:** There is a reasonable possibility that the study treatment, study drug, or study protocol caused the event.
- **Not Related:** There is no reasonable possibility that the study treatment caused the event. There may be other plausible alternative causes for the event which may include but are not limited to: medical history, lack of efficacy, worsening of treated condition, other treatment, concomitant medications, withdrawal of study treatment, or erroneous administration of treatment.

10.1.2 Serious Adverse Events (SAE)

All SAEs that occur from the time of signed ICF through the study termination visit (+/- 2 days) should be reported. Any SAE that is continuing at the time of the study termination visit will be followed until the outcome of the event is known. Whenever possible the investigator should report the overall diagnosis of the event(s) rather than the signs and symptoms associated with the event(s). Treatment or intervention of an event should not be reported as an SAE. The event necessitating treatment or intervention should be reported.

10.1.2.1 SAE Definition

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

1. Results in death.
2. Is life threatening.
3. Requires inpatient hospitalization or prolongation of an existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly or birth defect.
6. Is an important medical event (event does not result in death or is life threatening, but based on medical judgement may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above).

Life Threatening: is an event that in the view of the investigator places the participant at immediate risk of death from the event as it occurred (e.g., anaphylaxis, ventricular fibrillation, respiratory arrest). This does not include events which hypothetically might have caused death if it were more severe.

Hospitalization or Prolongation of Existing Hospitalization: An event that requires hospitalization or prolongation of an existing hospitalization. Hospitalization does not include the following: emergency room visit (< 24 hour) or same day surgeries (as outpatient/same day/ambulatory procedures, if the surgery was preplanned prior to entering the study). If during a preplanned hospitalization, an event occurs that was not part of the preplanned hospital admission (e.g., thromboembolic event), then the event prolonging the hospitalization and not the diagnosis or event associated with the preplanned hospitalization should be reported.

10.1.3 Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is a serious or non-serious event of scientific and medical concern specific to the study intervention. The event may require further investigation and depending on the nature of the event, submission to the FDA or other applicable regulatory authorities. For the purpose of this trial, AESIs have been predefined.

AESIs will be reported on the SAE/AESI report form within 24 hours of discovery. Any AESI that also meets the criteria of a SUSAR (suspected unexpected serious adverse reaction) will be emergently reported to FDA and other appropriate regulatory agencies, PIs, IRBs and IECs. AESIs will be followed until the outcome of the event is determined.

AESIs will include the following:

- Cardiac arrhythmias, or AEs that are indicative of QT interval prolongation, including (but not limited to) Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, palpitations, and non-postural syncope
- Cardiac disorders (e.g., acute MI, angina pectoris, ischemic chest pain)
- Drug diversion, drug abuse and drug accountability (e.g., accidental poisoning, behavioral addiction, dependence, drug abuser, drug diversion, overdose, intentional overdose, intentional product misuse, poisoning deliberate, prescribed overdose, substance abuser, euphoria-like response, hallucination dissociative state, psychosis, aggression, drug tolerance, habituation, drug withdrawal syndrome, substance related disorders)

- Central nervous system vascular disorders (e.g., ischemic central nervous system vascular conditions)
- Seizures
- Hypertensive crisis
- Suicide, suicidal behavior (e.g., intentional overdose, intentional self-injury, suicide attempt, suicide threat, suspected suicide, suspected suicide attempt), C-SSRS Suicidal Ideation score of 4 or 5, and/or suicidal ideation judged to be serious or severe in the opinion of the investigator

10.1.4 Other Reportable Information

Other reportable AEs include but are not limited to the following:

- Any clinically significant worsening of a pre-existing condition
- An AE occurring from an overdose (i.e., a dose higher than that indicated in the protocol) of study drug whether accidental or intentional
- An AE occurring from abuse (e.g., use for nonclinical reasons of a study medication)
- An AE that has been associated with the discontinuation of the use of a study medication
- A medication error such as an inadvertent or accidental exposure with or without an AE

Any event meeting the abovementioned listing should be reported on an SAE/AESI report form and sent to the sponsor or designee within 24 hours of discovery. These events should be followed until the events have subsided, returned to baseline or in the case of permanent impairment, until the condition stabilizes.

10.1.5 SAE and AESI Reporting

In the event of an SAE or AESI, the investigator must fill in the SAE/AESI Report form. The form should be signed and dated. The SAE form should be sent to the sponsor or designee within 24 hours of awareness of the event. Each event should have a separate SAE/AESI form.

The investigator should include the minimum reportable criteria on the SAE/AESI report form. The minimum criteria include: a product, a participant, a reportable event, and a site/investigator. If any of the reportable criteria are missing, the Principal Investigator (PI) should acquire the information prior to submitting the SAE/AESI form.

It is not necessary to send source documentation to the sponsor as part of the SAE/AESI reporting function but the documentation should be available on site. However, the sponsor may request source documentation associated with the event (e.g., hospital admission, relevant tests, and labs, discharge summary, autopsy report) and the site should be able to supply the documentation when requested.

If source documentation is requested, all source documentation must be de-identified, redacted, or pseudonymized in all attached documents before being sent to the sponsor or designee. Any follow-up information should be provided on a new SAE/AESI report form with a sequential follow-up number starting with follow-up #1. The SAE/AESI report form should be used for any changes, revisions or additional report to the event.

The sponsor assumes responsibility for appropriate reporting of any suspected unexpected serious adverse reaction (SUSAR) to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or sponsor where required) must report these events to the appropriate Institutional Review Board (IRB) and/or IEC (Independent Ethics Committee) that approved the protocol unless otherwise required and documented by the IRB/IEC.

All SAEs and AESIs should be followed until resolved, returned to baseline or stabilized to a level satisfactory to the investigator.

10.1.6 Pregnancy Reporting

- Details of all pregnancies in participants and their partners will be collected after the start of study intervention and until the participant's final visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.
- Pregnancies should be reported on a pregnancy form.
- Pregnancies will not be considered SAEs. However, any pregnancy that meets the criterial of an SAE (e.g., still birth, spontaneous abortion) should be reported on both a pregnancy and SAE/AESI report form. The SAE form is due to the sponsor or designee within 24 hours of awareness of the event.
- Pregnancies will be followed until the outcome of the pregnancy is known.
- Live births will be followed for 30 days after delivery.

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

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

10.1.7 Participant Discontinuation or Withdrawal from Study

Reasons why a participant may discontinue or be withdrawn from the study may include but are not limited to:

- Development of toxicity which in the investigator's judgment precludes further therapy
- Participants request
- Participant non-compliance
- Intercurrent illness
- At the discretion of the investigator
- Pregnancy
- Study termination by the sponsor
- Protocol violation

When a participant is withdrawn, the investigator will notify the sponsor and clearly document in the medical record and appropriate case report form the reason for withdrawal from study. When possible, the investigator will perform the procedures indicated for the final visits within 30 days after the last medication dose.

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

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

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - PABP on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented non-surgical hysteroscopic sterilization (Essure)
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

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

10.3.2 Contraception Guidelines

Study participants who were assigned male at birth with partners able to become pregnant will not be required to practice contraception. Adequate contraceptive methods are required for participants able to become pregnant and 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

- Abstinence from penile-vaginal intercourse
    - The reliability of abstinence should be evaluated carefully with the participant in relation to their general lifestyle. An additional acceptable contraceptive method should be discussed with the participant in case they decide to engage in penile-vaginal intercourse during the course of the study.

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

10.3.3 Follow-up Requirements

Details of all pregnancies in study participants and their partners 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, PCL-5 assessments, and Study Termination procedures. At a minimum, prior to withdrawal from the study, efforts should be made to assess the final PCL-5 immediately and complete Study Termination procedures.

The investigator will collect follow-up information on the participant or their partner 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 Data Monitoring Committee

The sponsor will appoint a DMC with appropriate expertise in the conduct of clinical trials to independently monitor participant safety information during the study and make associated recommendations for all reviews. The DMC is an independent expert 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 DMC will include clinician experts and at least one biostatistician.

The objective of the DMC Charter is to outline the specific purposes and functions of the DMC. In addition, it describes the procedures for data abstraction and data delivery conventions to and from the DMC members for review purposes. Access to the DMC charter will be restricted to the DMC and only limited specified sponsor staff who were involved in the trial design.

The DMC will periodically receive safety reports as described in the DMC charter and at any time a Serious Adverse Reaction (SAR) occurs to assess suitability of continuation of the study based on the risk/benefit profile and make recommendations as necessary. The objective of the DMC safety review is to monitor the safety of the participants enrolled and to be enrolled in the study. The DMC will also review the results of other trials specified in their charter and make recommendations on updating the adaptive design elements of the study protocol or data analysis.

The DMC will communicate their recommendations to the sponsor study staff, who will implement accordingly.

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 opioids will be cross-tapered to an allowable opioid (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 or activity, with the Baseline PCL-5 at Preparatory Session 3 (Visit 3) scheduled to occur after complete washout for psychoactive medications and Experimental Session 1 (Visit 4) scheduled to occur after complete washout for medications with drug-drug interactions without a psychological concern (5 half-lives of parent drug or active metabolite, whichever is longer, 2 weeks for MAOIs, and 3 weeks for imipramine and clomipramine).

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 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, to avoid withdrawal effects of discontinuation between Experimental Sessions) or sleep aids (excluding trazodone) in compliance with Section 11.3 Prohibited Medications. Sublingual nitroglycerin will be available on site in the case of emergency.

Gabapentin or certain opioids will be allowed when prescribed for pain management. The following opioids will be allowed during the study: hydrocodone, morphine, and codeine. Prior to randomization, participants who are taking opioids not included on this list will be cross-tapered to an allowable opioid under the care of their prescribing physician. Opioid medications may reduce the effectiveness of MDMA and may prolong QT/QTc interval, but the opioids that are allowed during this trial have been selected because they have the lowest potential for QT/QTc interval prolongation and minimal serotonergic effects. Individuals using opioids 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 opioid 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

There are medications that should be discontinued prior to enrolling in the study. These medications should not be restarted until study termination unless previously discussed with the MPBC medical monitor.

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 opioids for pain control).
- Agree to follow an appropriate tapering initiated at enrollment visit, defined by the treating physician, and to respect a subsequent washout period of 5 half-lives of the medication (calculation based on parent or active metabolite half-life, whichever is longer) preceding Visit 3.
    - For specific medications, including antidepressants and most antipsychotics, refer to the Allowed and Prohibited Medication List (if a drug is not in the list, it will be discussed with the Medical Monitor).
    - For non-selective irreversible MAOIs, a 2-week washout period following the taper is required (three weeks in the case of imipramine and clomipramine, tricyclic antidepressants with MAOI activity) prior to Experimental Session.

Use of St. John's Wort, and other herbs and medicines with notable serotonergic effects are prohibited from Baseline to Study Termination.

Ketamine must be discontinued 1 month prior to Preparatory Session 3 (Visit 3) and is prohibited until Study Termination.

If an SSRI, SNRI, MAOI (including non-psychiatric medications with MAOI activity, e.g. rasagiline, selegiline, linezolid), or other antidepressant (including antipsychotics used for depression, e.g. clozapine, risperidone, aripiprazole, ziprasidone, olanzapine) is used between Experimental Session 1 (Visit 4) and Study Termination (Visit 16), the participant will be withdrawn from treatment and continue in follow-up.

Opioids other than hydrocodone, morphine, and codeine are prohibited from Enrollment Confirmation to Study Termination. Participants taking prohibited opioids will be cross-tapered to an allowable opioid during the Preparatory Period.

11.3.1 Prohibited Medications prior to the Experimental Sessions

There are medications that can be used during the protocol but should be held prior to the Experimental Sessions. The participant should agree to the following:

- Agree 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 for 5 half-lives of the medication (calculation based on parent or active metabolite half-life, whichever is longer) 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 contraception, thyroid hormones, anti-hypertensives, or other medications approved by the research team).

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
- Complete Blood Count (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
- Urine-dip pregnancy test for participants able to become pregnant will be performed at the site. Serum human chorionic gonadotropin (hCG) pregnancy test (if urine test is positive; for PABP only).
- 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 during the beginning of the study, which will provide more detail about analyses than provided in this protocol. A brief overview of the statistical analyses that will be performed is provided in the following sections.

13.1 Power and Sample Size Determination

This is a multi-site open-label safety extension study of MDMA-assisted therapy for the treatment of participants with PTSD. The effectiveness of MDMA-assisted therapy will be measured by the PCL-5 and SDS. The sample size is not determined by statistical criteria.

13.2 Statistical Analyses

Every effort will be made to ensure complete, accurate and timely data collection and to avoid missing data, to ensure the completeness of the data which can impact the integrity and accuracy of the final study analysis. The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS® Version 9.4. In general, nominal variables will be described in terms of frequencies and percentages. Ordinal and non-normal continuous variables will be described using the sample median, 25th and 75th percentiles, and interquartile range (IQR).

The following analysis set is defined for this study:

- **All Enrolled**: all participants who are enrolled in the study
- **Safety**: all participants who receive any IMP

13.2.1 Effectiveness Analyses

13.2.1.1 Primary Outcome

The primary analysis of the effectiveness of MDMA will be made using a Mixed Model Repeated Measure (MMRM) model to assess changes in PCL-5 scores throughout the study period from Baseline (Visit 3) through Visit 16. Baseline covariates (age, gender, ethnicity, index trauma, complexity and severity of trauma, diagnosis of comorbid depression, diagnosis of comorbid Axis 2 diagnosis, adverse childhood experiences collected in the parent study) may be assessed for inclusion in the final model with an alpha level set at 0.05. Details of analyses are described in the Statistical Analysis Plan.

13.2.1.2 Secondary Outcome

The SDS will be analyzed in a similar manner to the primary analysis of the PCL-5. Details of analysis are described in the Statistical Analysis Plan.

13.2.2 Safety Analyses

Safety analyses will confirm safety data with summary tables listing exposure to IMP, unsolicited AEs, TEAEs, 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. Compare 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 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.

13.2.3 Concomitant Medications

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). Additional details are available in the Statistical Analysis Plan.

13.2.4 Analysis of Exposure

The frequencies and percentages of participants with exposure will be summarized overall and by visit.

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 MPBC, including designing, initiating, managing, coordinating, continuing, and concluding the clinical trials within the Clinical Development Program. MPBC is tasked with maintaining the quality of study conduct through ongoing monitoring of data and participating in writing study publications. MPBC contracts with

independent entities who represent clinical sites to accomplish these goals. Collectively, MAPS and MPBC 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 ICH Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21) and with the ethical principles laid down in the Declaration of Helsinki.

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, Health Canada, or Israeli Ministry of Health) 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 team 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 maybe 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 an electronic ICF platform is available, it may be used. If no electronic ICF platform is available or there are technical difficulties, the participant will sign a paper copy of the ICF during that telemedicine visit. The participant will then submit a scan or image of the ICF to the site and 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 teams, and all study staff will be trained prior study start for each site. Study sites will be monitored by remote monitoring and/or 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.

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 securely at the study site and the sponsor may be given view only access through a secure electronic document storage system to facilitate remote monitoring.

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. Except for the Informed Consent, previous medical records, emails with the participant, and a Contact Information Sheet that will be stored separately from other documents, all source data will be identified only by the participant's initials and SUBJID. 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, Health Canada Guidance for Records

Related to 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 or secure electronic document storage system, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators and sponsor staff 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.

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 helpful 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 video data 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. Patients who previously received therapy from a therapy team 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 ICF.

14.5 Treatment and Compensation for Study Related Injury

If a participant becomes sick or injured during the study, they should call the site physician. 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 injury, sickness, or emergency would first be billed to a participant's health insurance provider, if the participant has health insurance. If the participant's private or employer health insurance plan does not cover clinical trial-related claims that occurred during the course of the study, then the sponsor will cover any treatment costs directly related to the study. To cover these costs, the sponsor carries third-party insurance.

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.

14.6 Record Retention

Investigators must retain all study records required by the sponsor and applicable ICH-GCP and FDA regulations, and Health Canada Guidance for Records Related to Clinical Trials (GUIDE-0068) 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.

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.

15.0 Appendix A: Sub-study without Overnight Stays

Rationale

This sub-study to the MAPPUSX protocol "A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Therapy for the Treatment of Participants with Posttraumatic Stress Disorder" allows participants to be discharged in the evening after the Experimental Session is over at select investigational study sites. In MAPS' Phase 2 study MAA1, which tested the safety and efficacy of MDMA-assisted therapy for social anxiety among autistic adults, an overnight stay was not required. This approach was also tested in the Phase 2 study MP16 and Phase 3 study MAPP1 with no safety concerns due to travel to home or hotel; this approach was found to be comparable in safety to participants who had an overnight stay. The sub-study has also been tested in the Phase 3 study MAPP2. The accumulation of these sub-study samples will enable a sample size to permit an integrated analysis of safety for this protocol variant compared to participants with an overnight stay.

Study site and participants will follow all protocol procedures described in the main protocol, except those related to overnight stays as described below. The overnight stay is included in the main study protocol primarily as an opportunity for rest and integration in a relaxed and comfortable environment away from the distractions of home, and to facilitate the logistics of participation in the integrative visit at the site on the day following the Experimental Session. The overnight stay is not required for medical reasons, but in case of emergencies, the therapists and study physician are on-call for all sites.

In the main study protocol, a Night Attendant accompanies the participant during the overnight stay. The Night Attendant's primary function is to ensure the participant is comfortable and has a meal, to provide minimal support, and to alert qualified site staff in case of need expressed by the participant or determined by observation. All Night Attendants are interviewed, trained, and approved by therapy teams to ensure they are comfortable providing the necessary support and know whom to call if medical support is needed from the therapy pair or study physician.

Medically-trained Night Attendants have not been required for any of the five Phase 2 studies of MDMA-assisted therapy for PTSD since MP-1 was completed. In MP-1, the first Phase 2 study, the FDA required that the Night Attendant be a registered nurse. Since MP-1, Night Attendants were not required to have medical training in subsequent studies. Among 189 participants treated under this IND, no medical complications have arisen during overnight stays under the watch of Night Attendants.

The sponsor and investigators agree that allowing participants who are screened for stable domestic circumstances to return home will not increase the risks of participation in the study. The study protocol discusses the risk of psychological distress in a PTSD population and mitigation in Section 9.2.2.2 Psychological Risks and Mitigation. Therapists and site physicians are aware of these risks, including anxiety and depressed mood occasionally reported 1 to 3 days after MDMA administration. In previous Phase 1 and 2 studies, these reactions have been transient and have responded well to reassurance from the therapy pair, with occasional use of benzodiazepines for anxiety. If needed, the study physician may prescribe a short-acting, low-dose benzodiazepine (specifically, lorazepam) or sleep aids (excluding trazodone) as needed.

Consistent with the main study protocol and the sub-study, 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).

- Excluding people who do not have a stable living situation or supportive family/network.
- 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.
- Conduct of Integrative Session on the morning after the Experimental Session.

Specific to sub-study:

- Therapist phone contact with participants on the night of the Experimental Session.
- A support person identified by the participant and agreed upon by the therapist must stay with the participant overnight on the evening following the Experimental Session.
- The therapists will meet with the support person prior to the first Experimental Session to assess their ability to act as an appropriate support person and to give them instructions about what to expect following Experimental Sessions and how to contact study personnel if needed.
- A support person must assist the participant during transfer from study site after the Experimental Session and to the study site on the following morning for the Integrative Session. This Integrative Session will start later in the day to allow for logistics of transportation. Participants can arrange their own transportation after the Integrative Session. The Integrative Session may happen remotely if approved by the research team.

Implementation of Sub-study

All eligibility criteria from the main study protocol will apply, except for the following inclusion criteria listed as a Lifestyle Modification:

Post Experimental Session

- Are willing to remain overnight at the study site after each Experimental Session until after the Integrative Session the next morning (for exceptions see Appendix A sub-study)
- Agree not to drive after the Experimental Sessions until after the Integrative Session the next morning.

Sub-study participants will be required to be willing to:

Post Experimental Session

- Identify a support person willing to accompany them overnight at a safe location of their choice after each Experimental Session.
- Have the support person escort them away from the study site in the evening after the Experimental Sessions and to the site on the following morning for the Integrative Session. The Integrative Session may happen remotely if approved by the research team.

Screening & Preparatory Periods

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

the role. An escort who is responsible only for transportation need not meet with the therapy pair to perform that role. The participant will provide contact information for the appropriate support person(s) in advance of each Experimental Session.

Orienting the Support Person

In advance of the appropriate Experimental Session, the support person staying with the participant overnight will be required to meet with the therapy pair in person. The support person will receive printed instructions, including contact information of the study physician, therapists, investigator, and Study Coordinator and what to do in the case of an emergency.

The support person will not provide therapy to the participant. Minimal discussion is acceptable, but only if initiated by the participant. The support person should not interpret the participant's experience or act as therapist. The therapy pair will discuss this explicitly with the support person and include this information in the written instructions.

The main roles of the support person include:

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

End of Experimental Sessions

Consistent with the main protocol, at the end of each Experimental Session, the therapy pair and site physician will assess the participant to decide if they are physically and emotionally stable. If the participant is not stable, the therapy pair and/or site physician will stay with the participant until stable or escalate for further care as appropriate. If it is in the best interest of the participant for them to spend the night at the study site, the therapists will ensure an appropriate stay is provided.

In the sub-study, if a participant is deemed medically and psychologically stable by the therapy pair at the end of the Experimental Session, the participant will be escorted home via car, rideshare, or public transportation and will not remain overnight at the study site. The support person will be provided with an instruction sheet including how to contact the Clinical Investigator, Site Physician, and/or therapy pair to report any issues. The support person will stay overnight with the participant and be instructed to call 911 in the case of a psychiatric or medical emergency.

Each participant will be instructed to call the therapy pair when they arrive where they will stay for the night. If the therapy pair has not received a call within 2 hours after the participant has left the site, the therapists will call the participant and support person to confirm arrival. The therapy pair will ask about the participant's emotional well-being and invite them to begin the process of integration through self-reflection, journaling, meditation, or other quiet activities. The therapy pair will remind the participants that this evening should be an opportunity to rest and integrate and that they should avoid unnecessary stresses, chores, etc. The therapy pair will also discuss this with the participant during the Preparatory and Experimental Sessions. The therapy pair and site physician will remain on-call overnight to attend to any medical or psychological issues that may come up for the participant.

In the sub-study, if a participant is deemed to be not psychologically stable at the end of the Experimental Session, they will remain under the care of their therapy pair. The therapy pair will continue to evaluate the participant to make further disposition recommendations depending on the participant's psychological condition. This could include: continued observation, psychological support and/or psychopharmacologic interventions; or further evaluation for potential transfer as appropriate per site Standard Operating Procedures (SOPs). If the therapy pair determines that the participant needs ongoing observation and psychological care at the same location as the Experimental Session, there will be the option for them to remain overnight with the therapy pair in accordance with site SOPs. If the participant will not be leaving the site for the night, the therapy pair will call the support person(s) to inform them and arrange appropriate transportation following the Integrative Session on the following day if appropriate.

Sub-Study Objective & Evaluation

The primary objective of this sub-study will be to evaluate the feasibility of conducting MDMA-assisted therapy for PTSD among participants who do not remain at the study site overnight after Experimental Sessions.

This sub-study will include all participants enrolled and treated at select study sites. No formal analysis is planned to support this objective due to small sample size. However, case reports and AEs collected on the night of the Experimental Session will be evaluated to support feasibility. These reports will be used to explore feasibility of expanding the sub-study to include additional clinical sites and to support generalizability of potentially delivering this treatment to varied treatment settings post-approval.

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