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**Protocol and Synopsis MT2
IND #063384**

Original Protocol Version 1: 14 March 2019
Original Protocol Version 2: 20 May 2019
Amendment 1 Version 1: 27 August 2019
Amendment 2 Version 1: 27 December 2019

**A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted
Psychotherapy when Administered to Healthy Volunteers**

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USE	In conjunction with relevant regulatory and ethical guidance

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MT2 Protocol Synopsis **Protocol Amendment 2 Version 1: 27 December 2019**

Title

A Phase 1, Open-Label, Multi-Site Study to Assess Psychological Effects of MDMA-Assisted Psychotherapy when Administered to Healthy Volunteers

Study Code

MT2

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Rationale

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

MDMA is a monoamine releaser and re-uptake inhibitor with indirect effects on neurohormone release. The combined neurobiological effects reduce defenses and fear of emotional injury, enhance communication and introspection, and increase empathy and compassion. MDMA may enhance fear extinction learning in humans. The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process. Data from an international series of Phase 2 pilot studies of MDMA-assisted psychotherapy conducted by the sponsor provide preliminary evidence that chronic PTSD, independent of cause, is treatable with two to three sessions of MDMA-assisted psychotherapy and associated non-drug preparatory and integrative psychotherapy. Ongoing Phase 3 studies are intended to demonstrate the efficacy and safety of manualized MDMA-assisted psychotherapy as a treatment for PTSD.

The Phase 1, randomized, placebo-controlled study (MT1) was designed to collect safety and quantitative data on mood, psychological symptoms, personality traits, and interpersonal closeness in trainees learning to conduct MDMA-assisted psychotherapy or MDMA research.

The MT1 study was also designed to expand the knowledge of trainees learning to conduct MDMA-assisted psychotherapy research, primarily those who would be working on a study with a placebo-control arm in their research setting. In the MT1 study, several participants submitted optional written narratives with impressions that participating in MDMA-assisted psychotherapy helped them professionally and personally. In addition, survey data was gathered from 79 of 82 MT1 participants reporting minimal risk of harm, with substantial potential for professional and personal benefit. In this survey, participants reported that their experiences in MT1 enhanced their therapeutic qualifications to administer MDMA-assisted psychotherapy to chronic PTSD patients.

This Phase 1, open-label, multi-site research study (MT2) is not a registration study. The MT2 study is designed to build upon the MT1 study and will enroll 150 participants in the United States (U.S.) to further assess the psychological effects and safety of manualized MDMA-assisted psychotherapy in healthy trainees who are learning to conduct MDMA-assisted psychotherapy or MDMA research. This study will also support expansion of the trainees' knowledge of the subjective effects and therapeutic potential of MDMA-assisted psychotherapy and enhance their qualifications to provide that therapy.

There will be a planned interim analysis for safety by internal review after 50% of participants are treated. This study is intended to look further into the personal and professional benefits spontaneously reported in narratives to the site team from the MT1 study participants. This will be done by collecting and assessing changes in self-compassion, burnout, professional quality of life, psychological inflexibility, and mood using validated measures in a larger sample of participants, allowing for effect size calculations. Compassion fatigue and burnout are associated with job-related stress and are known to impact professional quality of life. In addition, continued training for new treatment providers, including the option for their own MDMA experience, is vital as the research for MDMA-assisted psychotherapy for PTSD expands.

Study Description

A qualified study investigator or designee will discuss the study with potential participants and perform the consenting process. If the participant agrees, this process may be observed by a trainee who is enrolled in or has completed the MDMA Therapy Training Program under the auspices of the sponsor. After consenting, participants will enter the Screening period, which may also be observed by a trainee. This consists of an eligibility assessment and enrollment after meeting all inclusion criteria without meeting any exclusion criteria. Participants will be asked to complete study measures throughout their participation in the study.

A psychotherapy visit will be conducted prior to and after the MDMA-assisted psychotherapy session. All psychotherapy sessions will be conducted by at least one trained, qualified, and licensed facilitator holding a certificate from the MDMA Therapy Training Program. Either another MT2 facilitator, or a co-facilitator-trainee (who is enrolled in or has completed the MDMA Therapy Training Program under the auspices of the sponsor), will also be present in the psychotherapy sessions. Reference Lead Facilitator and Co-Facilitator Qualifications (Protocol Section 4.2.2) for more details on the requirements of these roles. Participants may also opt to include a support person in their sessions, if the facilitator agrees.

MDMA-assisted psychotherapy employs a largely inner-directive therapeutic method and is described in detail in the Treatment Manual. The inner-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.

The participant will be contacted at 2, 7, and 60 days after their MDMA-assisted psychotherapy session to follow-up on safety and complete study measures. A trainee may also observe these follow-up calls, if both the participant and facilitator agree.

Dose Selection

Participants will receive an initial dose of 120 mg MDMA (as the hydrochloride salt or "HCl", referred to as MDMA throughout), followed by an optional supplemental dose of 40 mg or 60 mg MDMA dose (based on drug availability and clinical judgement) administered 1.5 to 2 hours later.

This MDMA dose is in use in ongoing Phase 3 and previous Phase 2 MAPS-sponsored studies. The initial active dose is expected to produce all of the commonly reported effects of MDMA. The supplemental dose will prolong subjective drug effects without producing physiological effects significantly greater than peak effects occurring after the initial dose.

Measures

Primary Outcome Measure: Self Compassion Scale (SCS)

Exploratory Outcome Measures: Acceptance and Action Questionnaire-II (AAQ-II), Positive and Negative Affect Schedule (PANAS), Professional Quality of Life Scale (PROQOL), Maslach Burnout Inventory–Human Services Survey (MBI-HSS)

Safety Measures: Columbia Suicide Severity Rating Scale (C-SSRS), Vital Signs, Adverse Events (AEs), and Concomitant Medications

Screening Measures: Mini-International Neuropsychiatric Interview (MINI)

Protocol Objectives

The overall objective of this study is to explore the safety and psychological effects of open-label manualized MDMA-assisted psychotherapy in healthy volunteers using validated measures, and to expand the knowledge and qualifications of trainees who are learning to conduct MDMA-assisted psychotherapy or MDMA research. This study will also provide additional Phase 1 healthy volunteer data.

Primary Objectives

The primary objective of this study is to evaluate effectiveness of MDMA-assisted psychotherapy to change self-compassion in participants based on comparison of mean SCS scores collected at Visit 1 and Study Termination (60 days after the Experimental Session).

Exploratory Objectives

The exploratory objectives of this study are to evaluate effectiveness of MDMA-assisted psychotherapy to change:

1. Self-reported affect in participants based on comparison of mean PANAS scores collected at Visit 1 to Visit 3 (1 day after Experimental Session).
2. Self-reported psychological inflexibility based on comparison of mean AAQ-II scores collected from Visit 1 and Visit 3 (1 day after Experimental Session).
3. Self-reported professional quality of life in participants based on comparison of PROQOL scores collected at Visit 1 and Study Termination (60 days after the Experimental Session).
4. Self-reported burnout in participants based on comparison of MBI-HSS scores collected at Visit 1 and Study Termination (60 days after the Experimental Session).

Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs for MDMA-assisted psychotherapy in healthy volunteers. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy:

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

Recruitment and Subject Population

The investigative site staff will recruit persons aged 18 or older who are learning to conduct MDMA-assisted psychotherapy or MDMA research. Participants will be individuals who are either licensed, license eligible, pre-licensure, doctorate-level professionals, graduate students or researchers in a relevant field, individuals practicing in a related health care profession (e.g. physician, nurse, social worker), or other type of relevant practice approved by the MDMA Therapy Training Program.

Participants must meet all inclusion criteria, without meeting any exclusion criteria, in order to be eligible for study participation. Participants must be willing to commit to all study procedures and limitations on concomitant medications, if applicable. If the participant is of childbearing potential, they must have a negative pregnancy test and agree to use an effective form of birth control during the study. All participants must be proficient in reading and speaking the predominately used or recognized language of the study site.

Study Procedures

After giving written informed consent, candidates will be screened for eligibility, and up to 150 participants meeting study criteria will be enrolled with a planned interim analysis for safety by internal review after 50% of participants are treated. In consultation with their prescribing physician, any individuals taking prohibited study medications will taper off these medications in an appropriate fashion to avoid withdrawal effects. MDMA will be administered during the Experimental Session. Telephone calls will be made to the participant 2, 7, and 60 days after their Experimental Session to follow-up on safety and to perform applicable study measures. Preparatory, Experimental, and Integrative Sessions may be recorded to audio and video if the participant requests, for their own training purposes. The video will be provided to participants, but a copy will not be retained at the site.

At Screening, the participant will complete study measures and assessments, which will be reviewed by the site physician. The site will send an enrollment packet to the Medical Monitor to confirm eligibility. This should be done as early as possible in the screening period after all off-site assessments and measures are completed. If the Medical Monitor confirms the participant is eligible, the participant may continue in Screening with on-site assessments (urine drug screen, pregnancy screen [if applicable], and physical exam) and the site physician will confirm their eligibility after reviewing those results. Prior to beginning the Preparatory Session on Visit 1, the participant will complete the PANAS, C-SSRS, AAQ-II, SCS, PROQOL, and MBI-HSS. The participant will then undergo a 1.5-hour Preparatory Session with the facilitator team prior to the first Experimental Session in accordance with the Treatment Manual. During this visit, the facilitator team begins developing rapport with the participant and prepares them for MDMA-assisted psychotherapy.

The Experimental Session (Visit 2) will occur 1 to 7 days after the Preparatory Session. The participant will complete the C-SSRS before drug administration, and the facilitators will record any changes in medications. In addition, the facilitators will confirm that the participant has followed appropriate rules prior to drug administration. Each Experimental Session lasts approximately 8 hours. The participant will complete the C-SSRS at the end of the Experimental Session (6+ hours after drug administration). Following the Experimental Session, the participant will be allowed to go home or to a nearby location. If they are not stable or the facilitators feel it is in their best interest, they may stay at the study site. Participants must not operate a vehicle for at least 24 hours after the initial MDMA dose administration. They should arrange a driver or a transportation service (such as a taxi) to go to their destination.

On the morning after the Experimental Session, the participant will meet with the facilitators for a 1.5-hour integrative therapy session to discuss their experience. The participant will complete the PANAS, AAQ-II, and C-SSRS just prior to beginning the Integrative Session. At this non-drug psychotherapy visit, the facilitators will work with the participant to integrate the experiences from the Experimental Session and address any psychological distress that may have resulted.

Telephone calls will be made to participants three times (at 2, 7, and 60 days) after the Experimental Session to monitor safety, follow-up on any Adverse Events (AEs) or Serious Adverse Events (SAEs), and complete applicable study measures.

Safety

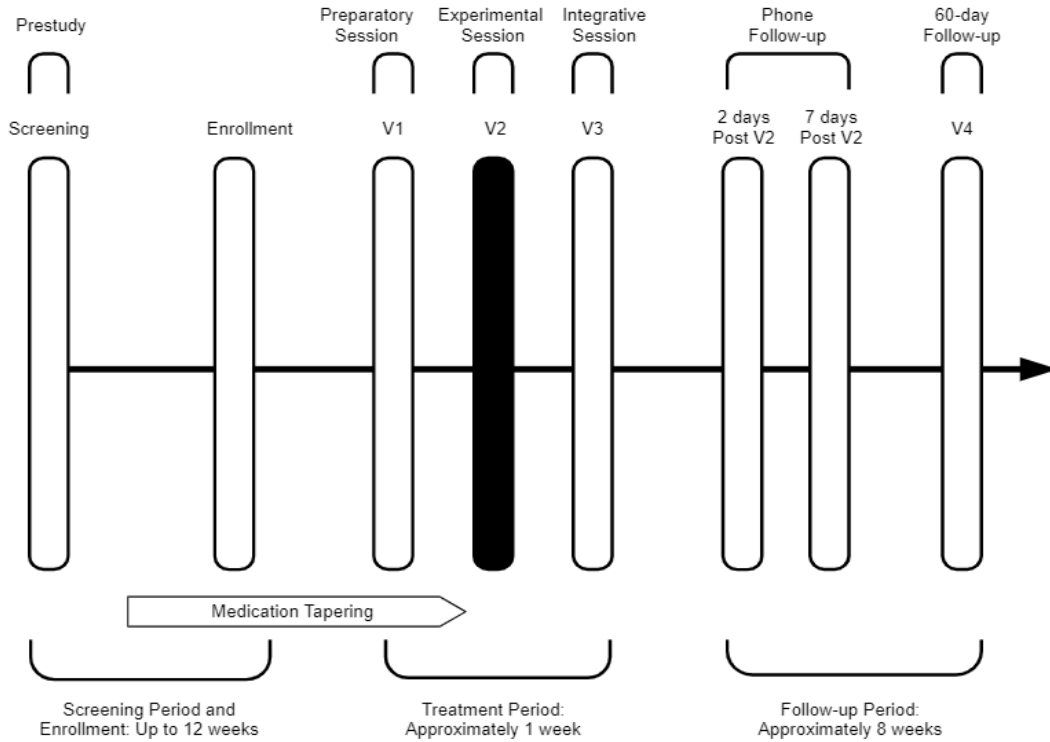
The safety of participants will be assured during and after the Experimental Session by assessing physiological vital signs, psychological distress, AEs, SAEs, and suicidality:

- Suicidality will be assessed with the C-SSRS at Screening, at the beginning of the Preparatory Session, twice during the Experimental Session (beginning and near the end), at the beginning of the Integrative Session, 2 days after the Experimental Session, and 7 days after the Experimental Session.
- Vital signs including blood pressure, heart rate, and body temperature will be measured at the following times throughout the day of the Experimental Session: prior to administration of the initial dose, once prior to administration of the supplemental dose, and at the end of the session (or until measurements return to near Baseline levels). The timing of these measurements will be adjusted so they do not interfere with the therapeutic process. Vital signs will be measured more frequently if there are 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.
- Serious Adverse Events (SAEs) will be collected from enrollment through Study Termination.
- All AEs will be collected on the day of enrollment through Study Termination including: clinically significant AEs requiring medical attention, any AE leading to withdrawal from the protocol, and AEs related to changes in psychiatric status.
- Events related to planned treatments or physician visits for Baseline conditions collected in the medical history will not be collected unless there is an exacerbation of the condition.

Statistical Analysis

The study will be conducted in N=150 participants with planned interim analysis for safety by internal review after 50% of participants are treated. Descriptive statistics and effect size estimates using Cohen's D One Group Pretest Posttest methods will be calculated for all measures. The primary outcome (SCS) and exploratory measures (AAQ-II, PANAS, PROQOL, and MBI-HSS) scores will be compared by performing a mixed model repeated measures analysis of variance (MMRM), with time of administration as repeated measure. Safety data, including incidence of AEs, suicidal ideation and behavior scores from the C-SSRS, and concomitant medications, will be presented as frequency tables. Mean changes in blood pressure, heart rate, and body temperature from pre-IMP administration to end of the Experimental Session will be compared.

Protocol Design Overview





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Original Protocol Version 2: 20 May 2019

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1.0 List of Abbreviations

AAQ-II	Acceptance and Action Questionnaire-II
ADHD	Attention Deficit Hyperactivity Disorder
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALT/SGPT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
API	Active Pharmaceutical Ingredient
AST/SGOT	Aspartate Aminotransferase
BA/BE	Bioavailability/Bioequivalence
BP	Blood Pressure
BT	Body Temperature
C	Celsius
cGMP	Current Good Manufacturing Practices
CI	Clinical Investigator
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
D.O.	Doctor of Osteopathic Medicine
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – IV
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl Methylcellulose
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	Independent Rater
IRB	Institutional Review Board
LSD	D-lysergic Acid Diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MBI-HSS	Maslach Burnout Inventory – Human Services Survey
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
M.D.	Doctor of Medicine
MDMA	3,4-methylenedioxymethamphetamine
MG	Milligrams
MINI	Mini-International Neuropsychiatric Interview
MMRM	Mixed Model Repeated Measures
MPBC	MAPS Public Benefit Corporation
PACS	Premature Atrial Contractions
PANAS	Positive and Negative Affect Schedule
PHI	Protected Health Information

PROQOL	Professional Quality of Life Scale
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PVC	Premature Ventricular Contractions
RACT	Risk Assessment and Categorization Tool
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
SAE(s)	Serious Adverse Event(s)
SCID	Structured Clinical Interview for DSM-5
SCS	Self-Compassion Scale
SNRI	Serotonin–norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment Emergent AEs
TSH	Thyroid Stimulating Hormones
U.S.	United States of America

2.0 Introduction, Background, and Rationale

2.1 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. MAPS Public Benefit Corporation (MPBC) is a wholly owned subsidiary of MAPS and is a key part of the MAPS strategy to become a sustainable non-profit organization.

MAPS has completed a series of Phase 2 studies designed to gather preliminary evidence about the safety and efficacy of MDMA-assisted psychotherapy in patients with posttraumatic stress disorder (PTSD). Based on these data, the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for MDMA-assisted psychotherapy for treatment of PTSD on August, 2017 [1]. This designation is reserved for drugs which demonstrate substantial improvement over available therapy in order to expedite the drug development process with the FDA. The designation was granted on the basis of examining the research that supported the two medications approved for use in treating PTSD, sertraline and paroxetine, effect sizes associated with treatment, drop-out rates and issues pertaining to reported side effects and treatment discontinuation. The effect size of MDMA-assisted psychotherapy is greater than that for paroxetine or sertraline and equal to that of psychotherapies, with lower rates of study drop out than reported for pharmacotherapies or psychotherapies, indicating a potentially favorable profile [1].

In 2019, MAPS published results showing clinically and statistically significant improvements in PTSD severity from 103 participants treated in six Phase 2 randomized, blinded pilot studies of MDMA-assisted psychotherapy in sites located in the US, Switzerland, Canada and Israel [2]. Comparison of PTSD symptoms between participants assigned to controls and participants assigned to active dose detected greater response in active dose participants, with a treatment effect size (Cohen's d) of 0.8, which is considered large. MDMA-assisted psychotherapy reduced PTSD symptoms in samples with various index traumas and in civilians, military veterans and first responders [3-5]. Findings from the long-term follow-up of MP-1 participants, occurring after all participants had received an active dose of MDMA, suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [6], and similar findings of enduring benefits were reported in subsequent sponsor-supported studies [3, 5, 7]. Findings from several pilot studies support improvement in PTSD symptoms after two or three sessions of MDMA-assisted psychotherapy [3, 5, 7, 8]. Long-term follow-up data collected at least 12 months later from these studies suggest that therapeutic benefits continued to increase for some of these participants.

A key limiting factor in the MAPS drug development plan is the need to train significant numbers of therapists to conduct MDMA psychotherapy research in accordance with the Treatment Manual [9]. MAPS is developing group and individual training programs to teach the techniques and procedures for conducting MDMA-assisted psychotherapy. The MDMA Therapy Training Program is designed to support and expand the knowledge and skills of future therapists who will conduct MDMA-assisted psychotherapy. Participation in a research study will provide therapists with a training opportunity and insight into the experience of MDMA in a therapeutic context, a better understanding of the techniques taught in the MDMA Therapy Training Program. Receiving MDMA-assisted psychotherapy will provide participants with an in-depth understanding of how to maximize the therapeutic effects of MDMA. It will also allow trainees to better assess the psychological safety profile of MDMA-assisted psychotherapy in comparison to background events related to medical history.

The Phase 1, randomized, placebo-controlled study (MT1) was designed to collect safety and quantitative data on mood, psychological symptoms, personality traits, and interpersonal closeness in trainees learning to conduct MDMA-assisted psychotherapy or MDMA research. The MT1 study was also designed to expand the knowledge of trainees learning to conduct MDMA-assisted psychotherapy research, primarily those who would be working on a study with a placebo-control arm in their research setting. In the MT1 study, several participants submitted optional written narratives with impressions that participating in MDMA-assisted psychotherapy helped them professionally and personally. In addition, survey data was gathered from 79 of 82 MT1 participants reporting minimal risk of harm, with substantial potential for professional and personal benefit. In addition, participants reported that their experiences in MT1 enhanced their therapeutic qualifications to administer MDMA-assisted psychotherapy to chronic PTSD patients.

This Phase 1, open-label, multi-site research study (MT2) is not a registration study. The MT2 study is designed to build upon the MT1 study and will enroll 150 participants in the United States (U.S.) to further assess the psychological effects and safety of manualized MDMA-assisted psychotherapy in healthy trainees who are learning to conduct MDMA-assisted psychotherapy or MDMA research. This study will also support expansion of the trainees' knowledge of the subjective effects and therapeutic potential of MDMA-assisted psychotherapy and enhance their qualifications to provide that therapy. There will be a planned interim analysis for safety by internal review after 50% of participants are treated.

This study is intended to look further into the personal and professional benefits spontaneously reported in narratives to the site team from the MT1 study participants. This will be done by collecting and assessing changes in self-compassion, burnout, professional quality of life, psychological inflexibility, and mood using validated measures in a larger sample of participants, allowing for effect size calculations. Compassion fatigue and burnout are associated with job-related stress and are known to impact professional quality of life. In addition, continued training for new treatment providers, including the option for their own MDMA experience, is vital as the research for MDMA-assisted psychotherapy for PTSD expands.

A comprehensive review of MDMA research is contained in the Investigator's Brochure (IB) supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

2.2 Background Information

2.2.1 Supporting Information

Previous research studies have shown that self-compassion may be linked to PTSD symptoms. In a study examining the within-person relationship of PTSD symptoms related to self-compassion components, PTSD symptoms ranked higher when initial self-judgement existed. In that study, results showed that self-compassion components maintained PTSD symptoms and implied the recommendation for an increase in self-kindness to treat PTSD [10]. Another study was conducted to research self-compassion with PTSD symptom severity. Results from this study supported the notion that persons with PTSD may improve by combining elements of self-compassion in their treatment plans [11]. Data from this healthy population MT2 study may indirectly cast some light on possible mechanisms in MDMA-assisted psychotherapy for PTSD.

Research into the subjective effects of MDMA has been spurred in part by the widespread use of Ecstasy (material represented as containing MDMA) in recreational settings. Early trials conducted in the 1990s investigated alterations of consciousness and mood after MDMA consumption [12, 13], and subsequent investigations assessed the subjective effects of MDMA with measures specifically designed to assess alterations in consciousness, such as the Addiction

Research Center Inventory, Altered States of Consciousness Scale, or Hallucinogen Rating Scale [14-17]. Previous research using healthy volunteers in clinical or neuropsychiatric laboratory settings has investigated alteration of consciousness and mood throughout the duration of drug effects and, on rare occasions, over a 24-hour period [15, 16, 18]. The assessments of mood often involved cognitive tasks, imaging or physiological assessment, and was conducted immediately before and during MDMA administration. Such studies report consistent findings of elevated positive mood, anxiety and slight alterations in perception, and reported feeling more talkative, friendly and energetic but also more tense and anxious over loss of control [16, 18]. It is notable that MDMA tends to produce elevations on most or all scales of alteration of consciousness, but that these measures do not permit specific or directional assessment of mood. Subjective effects reported in clinical trials differ from the richer reports provided from retrospective surveys of people using Ecstasy in various recreational settings, where people are more likely to report increased closeness to others or greater acceptance of self or others, as well as positive mood, anxiety, and slightly altered perception [e.g. 19, 20-22]. Findings from studies comparing the effects of MDMA with psychostimulants demonstrate that MDMA has a unique profile [23, 24].

Studies conducted after these initial studies focused on social cognition or autobiographical memories [25-28]. These studies confirmed prosocial effects of MDMA, including increased emotional empathy, increased prosocial behavior and greater tolerance for self-selected “worst” memories. These findings suggest that along with positive mood and mildly psychedelic effects, MDMA has a unique profile of subjective effects consonant with use in psychotherapy as a means of augmenting therapeutic alliance, increasing self-compassion, and changing or reducing response to emotionally charged memories, such as those that trigger fear, despair or other negative emotions.

There is also an increasing amount of evidence that a person may be influenced in their behavior and mental health status more so by how their thoughts and feelings relate to them than by the form they take on (such as how negative they are). This finding is demonstrated in many areas. For example, pain and psychosocial disability can be foretold more by avoidance of pain rather than the degree of it [29]. Psychological inflexibility can be described as the strict domination of ones’ psychological reactions above their chosen values and their contingencies in guiding their actions. This may occur when evaluative and self-descriptive thoughts are fused, and a person attempts to avoid unwanted internal events. This has an “ironic” effect to enhance a person’s distress, which may reduce contact in a present moment, and may decrease a person’s likelihood of selecting values-based actions. In this type of context, a person may feel negatively impacted or “rocked” by their uncontrollable internal experiences. Because MDMA has reported positive changes on mood, there is a likelihood that psychological inflexibility can be positively enhanced.

Professionals who are providing care for others can often incur changes to their professional quality of life and experience “burn-out” [30, 31]. Burn-out in a profession consists of exhaustion (emotionally, physically, and/or mentally) which is brought about by excessive and continued stress. This can often lead to the professional feeling less compassionate about their patients, which may impact the care the patient receives. The World Health Organization classified burn-out as an occupational phenomenon deriving from workplace stress left unsuccessfully managed [32]. Because this study includes participants who are professionals providing care for others, an important outcome we hope to establish is an increase in compassion and professional quality of life after their experience with MDMA-assisted psychotherapy themselves.

A psychotherapeutic context differs from clinical trials and nonmedical settings in a number of ways. Participants are specifically prepared for the experience prior to drug administration with the expressed goals of introspection and communication with the facilitators about their inner experience, including giving attention to any emotionally intense or upsetting material that may

arise. In MDMA-assisted psychotherapy for PTSD, for example, people are expected to engage with trauma-related thoughts and memories in an inner-directive but focused manner, with intermittent support from the therapists. Listening to music is often part of the experience, as is the option to use eyeshades during the session. Participants remain at the study site overnight (or appropriate location approved by site team) and work with the facilitators on the morning after a session, continuing to discuss and address their experience of the previous day. As such, the psychotherapeutic setting provides a great deal more structure than most recreational settings but less engagement and task completion than a laboratory setting, thereby increasing the likelihood of intense emotions and allowing the opportunity to process them if they occur.

Up to 150 participants learning to conduct MDMA-assisted psychotherapy or MDMA research will be enrolled in MT2. There will be a planned interim analysis for safety by internal review after 50% of participants are treated. There is a precedent for the view that it is valuable for therapists to have personal experience with the specific therapeutic techniques they are being trained to employ. Various therapeutic schools have a model of psychotherapy training that requires psychotherapists in training to undergo some or all elements of psychotherapy [33]. While currently there is controversy as to the significance and benefits of these experiences, sometimes referred to as “personal psychotherapy,” specific features of using psychoactive substances as adjuncts to psychotherapy support such experiences [34].

Practitioners of psychotherapeutic methods such as trauma-focused cognitive behavioral therapy, prolonged exposure therapy, and psychoanalysis consider their personal experience with those modalities to be a beneficial part of their training. However, in the case of present-day MDMA research, personal experience with MDMA can only be obtained legally through participation in a government-approved protocol. Some researchers currently conducting the MAPS MDMA/PTSD studies have expressed the opinion that it would enhance the treatment that they are able to provide to study participants if they were able to experience MDMA to better understand the psychoactive effects within a controlled protocol such as this one. This view was reinforced by the results on the survey MAPS conducted of 82 participants in MT1, with 79 respondents.

The potential value placed on personal experience is consistent with the views expressed by many of the early psychedelic therapists and researchers from the 1940s to the early 1980s, who used psychedelic sessions to train therapists. At least some therapists who underwent personal therapy reported a better understanding of their patients’ experience, including both the negative and positive effects of therapy. People who are unfamiliar with the effects of a given compound in a specific setting may hold inappropriate expectations or be unaware of aspects of the setting that may enhance or hinder therapeutic effects. Investigators who researched d-lysergic acid diethylamide (LSD) in the course of psychotherapy reported that therapists who took LSD gained better insight into their patients’ experiences during LSD-assisted psychotherapy and were thus better able to aid them [35-37]. 108 people with pastoral and counseling jobs received LSD up to three times in a therapeutic context as part of the “Training Project for Mental Health Professionals” conducted at the Maryland Psychiatric Research Center, as part of Dr. Albert Kurland’s Investigational New Drug (IND) for d-lysergic acid diethylamide [38]. This was initiated in order to enhance the ability of mental health professionals to work with people who discussed LSD experiences with them. Daniel Helminiak STL, Ph.D., LPC, a Professor of Psychology at the University of West Georgia, one of the original participants in the “Training Project for Mental Health Professionals”, reported long-term benefits to their ability as a therapist from undergoing a supervised experience with LSD [39].

This exploratory protocol will use the Self-Compassion Scale (SCS) to measure compassion changes, and the Positive and Negative Affect Schedule (PANAS) to measure current mood states and to examine potential changes in disposition. Psychological inflexibility will be assessed with

The Acceptance and Action Questionnaire-II (AAQ-II). Potential changes of professional quality of life will be measured by the Professional Quality of Life Scale (PROQOL), while changes in professional burnout will be measured by the Maslach Burnout Inventory – Human Services Survey (MBI-HSS).

2.2.2 Previous MDMA Research

As of October 2019, MDMA has been administered to 271 people in studies sponsored under a MAPS IND, and to 1329 individuals in clinical or research studies conducted without sponsor support that are published in scientific literature, giving a total of 1600 research participants exposed to MDMA. Unexpected and expected Serious Adverse Events (SAEs) involving administration of MDMA in MAPS-sponsored clinical trials have been rare.

The initial and supplemental doses of MDMA to be used in this protocol are similar in range to those in use in the studies of MDMA-assisted psychotherapy research completed in the U.S., Switzerland, Canada, and Israel. Previous researchers in studies not sponsored by MAPS have also used doses within this range [14, 16, 40-42].

2.3 Protocol Purpose

The purpose of this multi-site study is to collect quantitative data on mood, psychological status, self-compassion, professional quality of life, and professional burnout in healthy volunteers after MDMA administration within a therapeutic setting. This will be done through use of established measures (PANAS, AAQ-II, SCS, PROQOL, and MBI-HSS). This exploratory study will permit an understanding of the acute effects of the drug in a specific and relevant setting for use in therapy. This study will also gather additional information to support the safety profile of MDMA-assisted psychotherapy.

The psychotherapy method used on this study will be based on the MAPS Treatment Manual for MDMA-assisted psychotherapy. The Treatment Manual details descriptions of methods for therapists to provide guidance and support during MDMA-assisted psychotherapy. This treatment method can be conducted by therapists and researchers with or without any prior personal experience with MDMA, and MAPS will not require therapists conducting studies to have an experience with MDMA. This protocol will provide trainees who are engaged in learning to conduct MDMA-assisted psychotherapy or MDMA research with the opportunity to gain first-hand experience of the effects of MDMA administered in a therapeutic setting. Participation in this study could make a significant contribution to a therapist's effectiveness in conducting clinical trials with MDMA.

3.0 Protocol Objectives

The overall objective of this study is to explore the safety and psychological effects of open-label manualized MDMA-assisted psychotherapy in healthy volunteers using validated measures, and to expand the knowledge and qualifications of trainees who are learning to conduct MDMA-assisted psychotherapy or MDMA research. This study will also provide additional Phase 1 healthy volunteer data.

3.1 Primary Objectives

The primary objective of this study is to evaluate effectiveness of MDMA-assisted psychotherapy to change self-compassion in participants based on comparison of mean SCS scores collected at Visit 1 and Study Termination (60 days after the Experimental Session).

3.2 Exploratory Objective

The exploratory objectives of this study are to evaluate effectiveness of MDMA-assisted psychotherapy to change:

1. Self-reported affect in participants based on comparison of mean PANAS scores collected at Visit 1 to Visit 3 (1 day after Experimental Session).
2. Self-reported psychological inflexibility based on comparison of mean AAQ-II scores collected from Visit 1 and Visit 3 (1 day after Experimental Session).
3. Self-reported professional quality of life in participants based on comparison of PROQOL scores collected at Screening and Study Termination (60 days after the Experimental Session).
4. Self-reported burnout in participants based on comparison of MBI-HSS scores collected at Screening and Study Termination (60 days after the Experimental Session).

3.3 Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of AEs, AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs for MDMA-assisted psychotherapy in healthy volunteers. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy:

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

4.0 Protocol Design

This study protocol will use an open-label study design in 150 participants with a planned interim analysis for safety by internal review after 50% of participants are treated. A qualified study investigator or designee will discuss the study with potential participants and perform the consenting process. If the participant agrees, this process may be observed by a co-facilitator-trainee who is enrolled in or has completed the MDMA Therapy Training Program under the auspices of the sponsor. After consenting, participants will enter the Screening period and will

complete study measures and assessments.. The site will send an enrollment packet to the Medical Monitor to confirm eligibility. This should be done as early as possible in the screening period after all off-site assessments and measures are completed. If the Medical Monitor confirms the participant is eligible, the participant may continue in Screening with on-site assessments (urine drug screen, urine pregnancy screen [if applicable], and physical exam) and the site physician will confirm their eligibility after reviewing those results. The participant will be enrolled after meeting all inclusion criteria without meeting any exclusion criteria. Participants will be asked to complete study measures throughout their participation in the study.

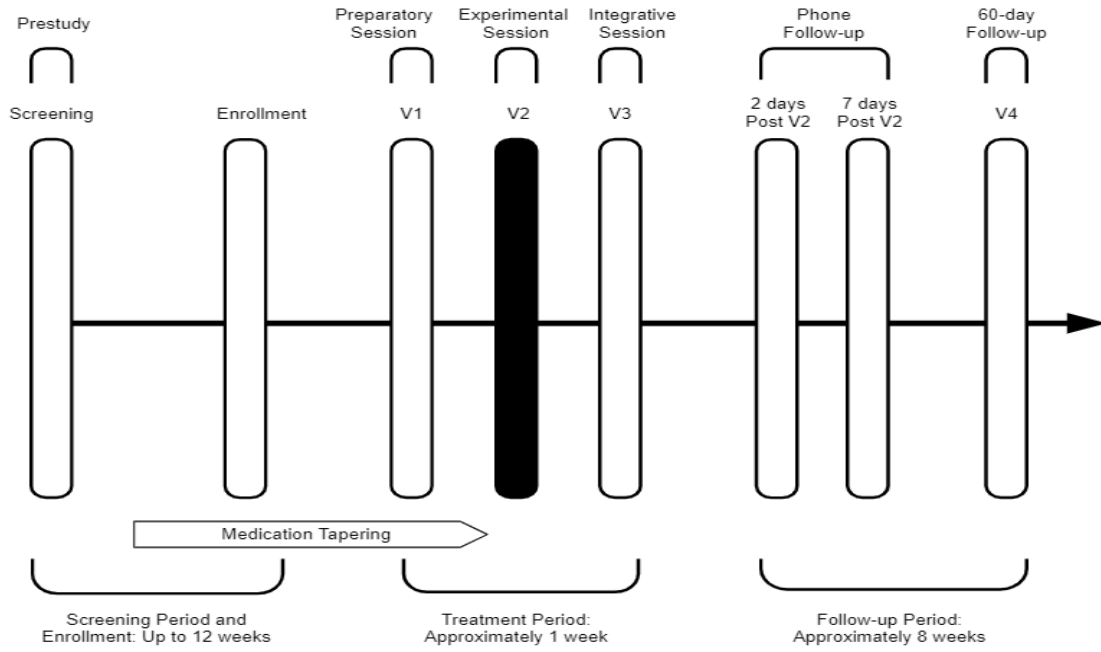
A psychotherapy visit will be conducted prior to and after the MDMA-assisted psychotherapy session. All psychotherapy sessions will be conducted by at least one trained, qualified, and licensed facilitator holding a certificate from the MDMA Therapy Training Program. Either another approved MT2 facilitator, or a co-facilitator-trainee (who is enrolled in or has completed the MDMA Therapy Training Program under the auspices of the sponsor), will also be present in the psychotherapy sessions. Reference Lead Facilitator and Co-Facilitator Qualifications (Protocol Section 4.2.2) for more details on the requirements of these roles. Participants may also opt to include a support person in their sessions, if the facilitators agree.

The facilitators will conduct one Experimental Session in approved treatment facilities, using a similar setting employed in Phase 2 and 3 studies of MDMA-assisted psychotherapy for PTSD. Participants will undergo a 1.5-hour Preparatory Session with the facilitators up to 7 days prior to undergoing the Experimental Session. The Experimental Session will take place at Visit 2. During the Experimental Session, participants will receive an initial dose of 120 mg MDMA followed by an optional supplemental dose of 40 mg or 60 mg MDMA (based on drug availability and clinical judgement) 1.5 to 2 hours later. Following the Experimental Session, the participant will be allowed to go home or to a nearby location. If they are not stable or the facilitators feel it is in their best interest, they may stay at the study site. Participants must not operate a vehicle for at least 24 hours after the initial MDMA dose administration. They should arrange a driver or a transportation service (such as a taxi) to go to their destination.

Each participant will have a 90-minute Integrative Session (Visit 3) on the morning after their Experimental Session. At this non-drug psychotherapy visit, study measures will be completed, and the facilitators will work with the participant to integrate the experiences from the Experimental Session and address any distress that may have resulted. All sessions may be recorded to audio and video if the participant requests, for their own training purposes. A copy of the video will not be retained at the study site.

Telephone calls will be made to participants three times (at 2, 7, and 60 days) after the Experimental Session to monitor safety, follow-up on any Adverse Events (AEs) or Serious Adverse Events (SAEs), and complete applicable study measures. A co-facilitator-trainee may also observe these follow-up calls, if both the participant and facilitators agree.

Figure 1: Protocol Design Overview



4.1 Planned Duration of Protocol

The total duration of study participation from Screening to Study Termination may be up to approximately 24 weeks (or about 6 months). Screening may take up to 12 weeks and active participation for the protocol psychotherapy sessions will be 3 days. Telephone follow-up visits will be conducted to monitor participant safety and perform applicable study measures at 2 and 7 days after the Experimental Session, and again 60 days after the Experimental Session (which will be the participant's Study Termination Visit). The protocol may remain active to allow for enrollment of 150 participants.

4.2 Clinical Investigator and Facilitator Qualifications

4.2.1 Clinical Investigator Qualifications

Each clinical site will include an appropriately qualified site Clinical Investigator (CI) who is personally responsible for the conduct of the study per the commitments they agree to in the FDA Form 1572. All CIs named in the IND are qualified by reason of their scientific training and experience to conduct the investigation described in the IND. The facilitators will work under the supervision of the site CI.

A Doctor of Medicine (M.D.) or a Doctor of Osteopathic Medicine (D.O.) will be designated as the CI or medical Co-lead CI (site physician) at each study site as previously requested by the FDA. The site physician will fulfill Drug Enforcement Administration (DEA) Schedule I license and FDA medical oversight requirements. Therefore, each site will have appropriately qualified personnel who will be licensed to manage and administer Schedule I controlled substances and may authorize a delegate (per DEA requirements) to administer drug under their license. The site physician conducting the screening may delegate screening to qualified site personnel such as a second site physician, nurse practitioner, or physician's assistant. The CI, or other delegated site physician, will review safety data during the ongoing conduct of the study and be responsible for reporting AEs to the sponsor. The CI, or other delegated site physician, will be on call and able to respond in case of a medical emergency during the Experimental Session.

4.2.2 Lead Facilitator and Co-Facilitator Qualifications

Two facilitators will be present with the MT2 participant for each on-site study visit after enrollment. The MT2 study staffing requirements are comparable to those requirements specified by the FDA in MAPS-sponsored Phase 3 trials:

- One person licensed to manage and administer controlled substances for each site
- A physician to assess participant safety at Screening
- One or more two-person therapy teams, male/female preferred
- One person per therapy team is required to be licensed to provide psychotherapy according to state and local requirements.
- If one person on the therapy team is unlicensed, they will work under the direction of the lead facilitator and within the delegation of authority of the CI.

The lead MT2 facilitator is required to be licensed to practice psychotherapy according to state and local requirements. For example, this could include a physician, a Ph.D. or Masters-level psychotherapist, or a registered nurse if their licensing board allows psychotherapy, and documentation is provided to support this. The MT2 co-facilitator may either meet the same lead facilitator qualifications, or (if working under the direction of the licensed lead facilitator) must

have a bachelor's degree and training in mental health, which includes students in a postgraduate internship-type program providing detailed knowledge of mental health interventions and treatments, or 1000 hours of behavioral health experience in addition to the MDMA Therapy Training Program.

The MT2 protocol allows for assistance from a Co-facilitator trainee if the MT2 study participant agrees. The role of the Co-facilitator-trainee is primarily to assist the facilitator in modeling the process of MDMA-assisted psychotherapy in a clinical setting, including the Preparatory, Experimental, and Integrative psychotherapy sessions at a minimum. Trainees must be enrolled in or have completed the MDMA Therapy Training Program under the auspices of the sponsor and will have documentation of this training, i.e. registration in the sponsor's online learning portal for Therapy Training. The trainees will meet all co-facilitator qualifications specified by FDA as required to work on approved MAPS-sponsored studies, as referenced above. The Co-facilitator-trainees will act under the direction of the lead MT2 facilitator. The lead MT2 facilitator will supervise the MDMA-assisted sessions, modeling the core principles of MDMA-assisted psychotherapy. The lead MT2 facilitator, site physician, and Schedule 1 license holder are responsible for participant safety and handling of the IMP, per Schedule 1 regulations. Co-facilitator-trainees agree to abide by the guidelines of the MDMA-Assisted Psychotherapy Code of Ethics in their interactions with MT2 participants, including maintaining confidentiality and professional boundaries.

The sponsor may approve lead facilitators to conduct MT2 sessions together with a co-facilitator trainee. If an MT2 participant declines having a Co-facilitator-trainee present, their sessions will be conducted with a team consisting of an MT2 lead facilitator and co-facilitator.

4.3 Experiential Learning for Co-facilitator-Trainees

The Co-facilitator-trainee will meet with the MT2 facilitator for an orientation to establish familiarity and review the process and roles. During the orientation meeting, the facilitator should inform the Co-facilitator-trainee of the site's procedures in case of an emergency. The MT2 facilitator orients the Co-facilitator-trainee on the process of screening and models the research process while conducting the MT2 protocol, so that the Co-facilitator-trainee may learn how to deliver MDMA-assisted psychotherapy in a clinical research setting while interacting with the MT2 study participant.

The sponsor's MDMA Therapy Training Program is designed to teach competency in applying MDMA-assisted psychotherapy. Training in the psychotherapy method consists of reading the Treatment Manual, completing an online training module, and participating in an in-person training program that includes watching and discussing videos of selected study visits which include psychotherapy. The required elements of the therapy are defined in the Treatment Manual of MDMA-assisted psychotherapy for treatment of PTSD.

4.4 Recruitment and Participant Population

The investigators will recruit individuals aged 18 or older who meet the inclusion criteria and do not meet any exclusion criteria, and who are engaged in learning to conduct MDMA-assisted psychotherapy or MDMA research through the MDMA Therapy Training Program. Participants will be individuals who are either licensed, license eligible, pre-licensure, or doctorate-level professionals, or graduate students or researchers in a relevant field, or individuals practicing in a related health profession (e.g. physician, nurse, social worker) or other type of relevant practice approved by the MDMA Therapy Training Program. Recruitment will be conducted by invitation only.

4.4.1 Inclusion Criteria

Individuals eligible to be enrolled into this protocol are participants who:

1. Are learning to conduct MDMA-assisted psychotherapy or MDMA research through the MDMA Therapy Training Program.
2. Are at least 18 years old.
3. Are willing to commit to medication dosing (including swallowing pills), study session attendance, and evaluation instruments.
4. Are willing to taper off of prohibited medications prior to Visit 1, and refrain from use until permitted by the research team.
5. Agree that, for approximately 1 week preceding the Experimental Session will refrain from:
 - a. Taking any herbal or dietary supplement (except with prior approval of the research team).
 - b. Taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen) unless with prior approval of the research team.
 - c. Taking any prescription medications (with the exception of prescribed contraception, thyroid hormones, or other medications approved by the research team).
6. Agree to take nothing by mouth except alcohol-free liquids and approved medications after 12:00 A.M. (midnight) the evening before the Experimental Session.
7. Agree not to use caffeine or nicotine for 2 hours before and 6 hours after initial drug administration.
8. Agree to not operate a vehicle for at least 24 hours after initial drug administration. Participants must have transportation available after the Experimental Session and through the following day, for traveling back for the Integrative Session.
9. Are willing to be contacted via telephone for all necessary telephone contacts.
10. If of childbearing potential, must have a negative pregnancy test at study entry and prior to the Experimental Session and must agree to use adequate birth control (see section 9.2.2) from the time of enrollment through 10 days after the Experimental Session.
11. Must provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by the investigator in the event of an emergency or if the participant is unreachable.
12. Must agree to inform the investigator within 48 hours if any medical conditions occur or medical procedures are planned.
13. Are proficient in speaking and reading the predominately used or recognized language of the study site.
14. Agree to not participate in any other interventional clinical trials for the duration of this study.

4.4.2 Exclusion Criteria

Individuals not eligible to be enrolled into this protocol are those who:

1. Are not able to give adequate informed consent.
2. Are pregnant, nursing, or are of childbearing potential and not willing to practice an effective means of birth control.
3. Any participant presenting suicide risk, as determined through clinical interview and responses to C-SSRS will be excluded.

4. Have uncontrolled hypertension using the standard criteria of the American Heart Association (values of 140/90 milligrams of Mercury [mmHg] or higher assessed on three separate occasions)[43].
5. Have a history of ventricular arrhythmia at any time, other than occasional premature ventricular contractions (PVCs) in the absence of ischemic heart disease.
6. Have Wolff-Parkinson-White syndrome or any other accessory pathway that has not been successfully eliminated by ablation.

5.0 Study Measures

5.1 Primary Outcome Measure

The primary outcome for self-compassion will be measured by SCS scores. The SCS 26-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion and recognizing one's own flaws and suffering as part of common human experience [44]. Estimated time to complete is 10 to 15 minutes. Participants will complete the SCS measure at Visit 1 and again 60 days after the Experimental Session (their Study Termination Visit).

5.2 Exploratory Outcome Measures

The exploratory outcome for psychological inflexibility will be measured by AAQ-II scores. The AAQ-II is a 7-item self-report assessment designed to assess a specific model of psychopathology that emphasizes psychological inflexibility [29]. Higher levels of this inflexibility, as measured by AAQ-II, are related to greater levels of depression, anxiety, stress, and overall psychological distress [29]. The measure is expected to take about 10 minutes to complete. The AAQ-II will be completed at the beginning of the Preparatory Session and at the beginning of the Integrative Session.

The exploratory outcome for psychological effects on mood will be measured by PANAS scores. The PANAS is a 20-item self-report assessment of current mood state, showing relations between positive and negative affect with personality statistics and traits [45, 46]. Participants will complete the PANAS at the beginning of the Preparatory Session and at the beginning of the Integrative Session. The measure is expected to take between 5 to 10 minutes to complete.

The exploratory outcome for evaluating the professional quality of life will be measured by PROQOL scores. The PROQOL is a 30-item self-report assessment of an individual's positive and negative feelings towards those they help professionally and how compassionate the individual may feel towards them [47]. Participants will complete the PROQOL at Visit 1 and at Study Termination. The measure is expected to take between 5 to 10 minutes to complete.

The exploratory outcome for evaluating professional burnout will be measured by MBI-HSS scores. The MBI-HSS is a 22-item self-report assessment of an individual's professional exhaustion according to three scales: emotional exhaustion, depersonalization, and personal accomplishment [30]. Participants will complete the MBI-HSS at Visit 1 and at Study Termination. The measure is expected to take between 10 to 15 minutes to complete.

5.3 Safety Measures

As safety measures, vital signs will be assessed at the beginning of and during the Experimental Session. Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure, body temperature, and pulse will be measured at the outset of the Experimental

Session, once prior to administration of the supplemental dose, and at the end of the Experimental Session, or until measurements return to near Baseline levels. The timing of these measurements will be adjusted so they do not interfere with the therapeutic process. Vital signs will be measured more frequently if there are 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.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [48]. It consists of a “Baseline” form that assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions and can be administered during face to face interview or over the telephone. The C-SSRS will be administered during the following:

- During Screening
- At the beginning of the Preparatory Session
- At the beginning of the Experimental Session
- At the end of the Experimental Session (6+ hours post initial drug administration)
- At the beginning of the Integrative Session
- At the 2-day and 7-day post Experimental Session follow-up phone call
- At any time that the participant expresses suicidal ideation during the study

5.4 Screening Measures

Along with the clinical interview, the Mini-International Neuropsychiatric Interview (MINI) will be used at Screening by a centralized Independent Rater (IR) to assess for excluded psychiatric disorders and any current problematic patterns of alcohol or other substance use. This version of the MINI (7.0.2), a structured interview that was first developed in 1998 to be compatible with the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Disease (ICD) criteria for psychiatric illnesses [49], is now compatible with DSM-IV. 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 [50]. The MINI takes approximately 60 to 90 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 Structured Clinical Interview for DSM-5 (SCID) [50, 51] Testing on nonpsychiatric samples did not create false positives [49].

Table 1: Time and Events

Study Period & Sessions	Screening Period			Treatment Period			Follow-Up Period	
	Phone Screening	Screening	Enrollment	Preparatory Session	Experimental Session	Integrative Session	Phone Follow-up	60-Day
Visit Type/Number			V0	V1	V2	V3		V4
Visit Timing and Windows	Prior to Initial Screening	Up to 12 weeks prior to V1	(may occur over more than 1 day).	0 to 14 days post V0 ¹	1-7 days post V1	1 day post V2	2 days after V2 and 7 days after V2 (+3 days for the 7-day call only)	60 days (~8 weeks) after V2 (±2 weeks)
Initial Phone Screen	✓ ^F							
Informed Consent	Send Copy	✓ ^F						
Medical/Psychiatric History	✓ ^F	✓ ^F						
Past/Current Medications and Adherence	✓ ^F	✓ ^F	✓	✓	✓	✓	✓	✓ ^H
General Physical Exam with vitals		✓ ^G						
ECG with 1-minute Rhythm Strip		✓ ^G						
Clinical Laboratory Tests		✓ ^G						
Drug Testing		✓			✓ ^A			
Pregnancy Testing (if applicable)		✓			✓ ^A			
Assess Eligibility	✓	✓	✓					
Off-site Assessments to Sponsor for Enrollment Review/Confirmation		✓						
Study Enrollment			✓					
Medication Taper (if applicable)		✓ ^F	✓ ^F	✓ ^F				
Record to Audio/Video (if requested)				✓	✓	✓		
MINI by Independent Rater		✓ ^F						
PANAS and AAQ-II				✓ ^B		✓ ^B		
C-SSRS		✓		✓ ^B	✓ ^{B, C, D}	✓ ^B	✓	
SCS, BMI-HSS, and PROQOL				✓ ^B				✓
Collect AE/SAEs			✓	✓	✓	✓	✓	✓
MDMA-assisted Psychotherapy					✓			
Vitals (BP, Pulse Rate, and BT)					✓ ^{B, D, E, C}			
Non-drug 90-minute Psychotherapy				✓		✓		

^A Perform procedure and review results prior to drug administration. ^B Administer/Perform at beginning of session (prior to drug administration if applicable). ^C Administer/Perform at the end of the session (6+ hours post initial dose administration, if applicable) ^D Administer/Perform as needed. ^E Administer/Perform approximately 2 hours after drug administration, and before supplemental dose administration. ^F May be done remotely. ^G May be done by outside provider and results reviewed by site prior to V0. If the physical exam is performed by an external provider, it must be repeated on site prior to enrollment. ^H Only if related to AEs or SAEs. ^I Time may be extended due to tapering and wash-out needs, if applicable.

6.0 Study Procedures and Visits

6.1 Study Procedures and Visits Description

If the facilitator and participant agree, the consenting process, screening process, study visits, and/or follow-up calls may be observed, as appropriate, by a co-facilitator-trainee (who is enrolled in or has completed the MDMA Therapy Training Program under the auspices of the sponsor).

Participants may also opt to include a support person in the psychotherapy visit sessions (Visit 1, Visit 2, and Visit 3), if the facilitator agrees. All on-site visits (Visit 1, Visit 2, and Visit 3) may be recorded to audio and video if the participant requests, for their own training purposes. The participant should provide a storage device, such as an external hard drive or flash drive, to copy the recorded content directly after the session. The recorded content should not be stored on sponsor-provided equipment and neither MAPS, nor their affiliates, will have access to the recordings.

6.1.1 Screening

Prospective participants will be pre-screened by telephone according to a script approved by the Institutional Review Board (IRB) in order to ascertain if they meet basic eligibility criteria. All individuals who are pre-screened should be assigned a Screening Number and recorded on a central Screening Log and assigned to an investigative site based on location and availability. Once assigned, the potential participant will receive a copy of the Informed Consent Form (ICF) for review prior to their invitation for a consenting visit at their assigned investigative site.

The ICF review process with the facilitator and participant may be done remotely (such as by telephone or video call). Participants should be allowed sufficient time to decide their interest in the study, and if they are still interested in participation after reviewing the ICF, then they will be instructed to countersign the ICF at the same time. The participant will then be given a copy of the signed ICF.

After consenting to take part in the protocol, participants will be screened by the facilitator and site physician. The site physician may delegate medical screening activities to qualified site personnel such as a second site physician, nurse practitioner, or physician's assistant. Screening can occur over more than 1 day and up to 12 weeks prior to Visit 1. Additional time may be considered for medication tapering needs only (see section 6.1.2 Preparatory Session Visit 1). If a potential participant is deemed ineligible during screening, they will be classified as a Screen Failure and notified that they are not eligible for the study.

All of the following preliminary tests and procedures must occur during Screening, and may be performed remotely or off-site, in order to be considered for study eligibility:

- Medical history, demographics, and psychological history will be procured by interview. The interviewer may require consent to obtain any medical records deemed necessary to clarify or provide more information about medical history if needed.
- Suicidality will be assessed by administering the Baseline/Lifetime C-SSRS.
- Pre-study medications will be reviewed and recorded. Any participant who takes a prohibited study medication, which could interfere with the research, must consult with their prescribing physician to begin tapering off that medication.

- A physical examination may be conducted by a qualified external care provider (e.g., nurse practitioner, physician) who is not a member of the study team and evaluated by the site physician. The exam must include:
 - Blood pressure and pulse
 - Height, weight, and body temperature
 - Examination of head, eyes, ears, nose, and throat
 - Examination of skin, heart, lungs, abdomen, and extremities
 - Brief neurological exam (cranial nerves 2 to 12, sensory, motor, reflexes, and cerebellar function)
- Electrocardiogram (ECG) with 1-minute Rhythm Strip, which should be evaluated by a qualified physician and results reviewed by the site physician.
- Clinical laboratory assessments (see Section 11.0 Clinical Laboratory Assessments) to be performed by a laboratory of the participant's choosing, by the study's central laboratory (e.g. LabCorp, TriCore), or by another qualified laboratory. The results may be provided by the participant to the site for review by the site physician. The site physician will use a list of normal ranges to decide whether participants are eligible for the protocol and will indicate justification for admitting participants with abnormal values.

The CI and/or a site physician will review all preliminary screening assessment results, notes from interviews and discussions, medical records (if applicable) and measures against eligibility criteria. If, upon examination, there are questions raised about possible medical problems, the site physician may request additional tests, assessments, or measures as indicated. The site physician may also contact outside care providers with participant permission as needed.

Individuals with well-controlled hypertension, or a history or current diagnosis of Diabetes Mellitus (Type 1 or Type 2) who are otherwise in good cardiovascular health will be referred for exercise testing and carotid ultrasound by a cardiologist to assess for underlying cardiovascular disease. 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 and the Medical Monitor approves their participation. Participants with well-controlled hypertension should continue to take their current anti-hypertensive medicines as clinically appropriate.

If the potential participant has stable and appropriately treated HIV, the site physician will record and review medications used to treat or stabilize the disease to determine whether there is likelihood of drug-to-drug interaction with MDMA. The site physician will then consult with the Medical Monitor to confirm participant eligibility prior to enrollment.

Individuals with a history or evidence of liver disease will receive hepatitis serology testing, and the participant will be evaluated by a physician with expertise in evaluating and treating liver disease. If Hepatitis C serology is positive and the potential participant has not already been evaluated for possible treatment of Hepatitis C, 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 Hepatitis C is judged by this physician to be stable and of mild severity the person may be enrolled if there are no other contraindications.

If the CI determines that the participant is eligible after reviewing the preliminary screening assessments, the site will send all preliminary screening assessment information to the Medical Monitor to confirm eligibility. If the Medical Monitor agrees that the preliminary screening assessment results are suitable for eligibility, the site physician may initiate medication tapering according to Section 10.1 Prohibited Medications and Tapering Instructions and may proceed with the remaining screening assessments as follows, which are required to be performed on-site (at the research location):

- Perform a urine-dip pregnancy test for participants of childbearing potential.
- Perform a urinary drug test. Any positive urinary drug test findings that cannot be attributed to pre-approved concomitant medications or diet will be reviewed by the Medical Monitor.
- If the physical examination was conducted off-site during preliminary screening assessments, it must be repeated on-site by a qualified professional and evaluated by the site physician. The exam must include:
 - Blood pressure and pulse
 - Height, weight, and body temperature
 - Examination of head, eyes, ears, nose, and throat
 - Examination of skin, heart, lungs, abdomen, and extremities
 - Brief neurological exam (cranial nerves 2 to 12, sensory, motor, reflexes, and cerebellar function).

After the remaining on-site screening assessment results are obtained, the investigator will review all screening information to determine the participant's eligibility. If all of the inclusion criteria and none of the exclusion criteria are met, then the participant will be enrolled in the study, and issued a subject number. Data from potential participants who do not pass screening will not be entered in the electronic case report form (eCRF) but reason of ineligibility will be documented on the Screening Log.

The Screening Log and Subject Log will both be updated with the subject number and initials. After the latter process is complete, the investigator will schedule three clinical visits: The Preparatory Session (Visit 1), the Experimental Session (Visit 2), and the Integrative Session (Visit 3). If tapering medication is necessary, the Experimental Session will be scheduled to occur after washout is complete.

6.1.2 Preparatory Session (Visit 1)

The Preparatory Session may occur on the same day of enrollment or up to 14 days after enrollment. If the site physician has documented a medication tapering plan for the participant, additional time may be given prior to scheduling Visit 1 if wash-out requires longer than 14 days according to the tapering plan. Prior to beginning the Preparatory Session, participants will complete the PANAS, Since Last Visit C-SSRS, AAQ-II, SCS, PROQOL, and MBI-HSS. Assess continued eligibility per inclusion/exclusion criteria in Section 4.4.1 and 4.4.2.

The facilitators will confirm the participant continues to meet eligibility criteria and appropriate medication tapering has occurred. The facilitator will then record the session to video, if the participant requests. The participant will then participate in a 1.5-hour Preparatory Session in which the facilitator(s) will:

- Review what will happen during the Experimental Session, following standard procedures and techniques discussed in the Treatment Manual (these will be adapted for the present context in which the participant does not have a psychiatric disorder).
- Prepare the participant for the fact that it is not possible to predict the content of the upcoming Experimental Session, and that specific psychological issues and difficult emotions may arise.
- Remind the participant that difficult emotions, including grief, rage and fear or panic, may arise during the Experimental Session, and that sometimes the process can produce surprising and profound experiences even in people without any psychiatric conditions.

- Supply the participant with a set of rules and restrictions for conduct 24 hours prior to the Experimental Session.
- Advise the participant not to take anything by mouth except alcohol-free liquids and approved medications after 12:00 A.M. (midnight) the evening before the Experimental Session.
- Advise the participant to refrain from the use of any psychoactive drugs, with the exception of caffeine or nicotine, within 24 hours before the Experimental Session, and not to use caffeine or nicotine for 2 hours before and 6 hours after initial drug administration.
- Answer any questions or concerns the participants may have.
- Discuss goals for the Experimental Session.

All AEs and SAEs will be recorded from the time the participant is enrolled through Study Termination.

6.1.3 Experimental Session (Visit 2)

The Experimental Session (Visit 2) will occur 1 to 7 days after Visit 1 and will last approximately 8 hours (measured from 30 minutes before dosing through 7.5 hours after dosing). If one of the facilitators is not a physician, a site physician must be on call during the Experimental Session.

The following table provides a general schedule with approximate times for the study procedures during the Experimental Session.

Table 2: Schedule of Procedures for the Experimental Session

Approximate Time	Procedure or Action
9:30	Urine Pregnancy Test (if applicable), Participant Acclimated to Environment, C-SSRS, Urine Drug Screen
9:45	Baseline Blood Pressure, Temperature, Pulse
10:00	Drug Administration, Begin Video Recording if Participant Requests
12:00	Blood Pressure, Temperature, Pulse, then Optional Supplemental Dose
As Needed	Blood Pressure, Temperature, Pulse
15:30	C-SSRS, Blood Pressure, Temperature, Pulse

The participant will arrive approximately 30 minutes before the planned dosing. Continuing eligibility will be confirmed and, if applicable, a urine pregnancy test will be performed at the start of the Experimental Session. Urine drug screening will be performed prior to the beginning of the Experimental Session and any positive findings that cannot be attributed to pre-approved concomitant medications or diet will be reviewed by the Medical Monitor to assess compliance with ongoing eligibility criteria. A positive pregnancy screen is cause for withdrawal from the protocol, while a positive drug screen for prohibited medications will be reviewed by the investigator as a possible cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study.

The participant will complete the C-SSRS approximately 30 minutes before drug administration, and the investigator will record any changes in medication since last visit (including confirmation of medication washout).

Assess continued eligibility per inclusion/exclusion criteria in Section 4.4.1 and 4.4.2. If the participant continues to meet criteria and the participant reports that they followed appropriate rules and restrictions, the session will proceed.

In addition, the facilitators will confirm that the participant has followed all appropriate rules and restrictions (e.g., no food or alcohol-containing beverage after midnight), and then familiarize the participant with the space and equipment while also reviewing the goals and logistics of the session in accordance with the Treatment Manual.

At approximately 10:00 AM, the participant will receive the initial dose of 120 mg MDMA along with a glass of water or electrolyte containing fluid. The facilitators should also start recording the session to video, if requested by the participant. A supplemental dose of 40 mg or 60 mg MDMA (based on drug availability and clinical judgement) will be administered 1.5 to 2 hours after the initial dose in the absence of contraindications. The participant will sit or recline on comfortable furnishings with eyeshades and a playlist of music available if the participant wishes to use them. The participant will be encouraged to spend much of the time focusing attention on their inner experience without talking, but may speak to the facilitators whenever they wish, and will receive guidance and support as needed. If the participant has not spoken within 1 hour, the facilitator will inquire briefly about their experience.

Blood pressure, heart rate, and body temperature will be measured at Baseline prior to drug administration, prior to the supplemental dose administration, or approximately 2 hours into the session if the supplemental dose is not going to be administered. A final measurement of blood pressure, heart rate, and body temperature will be taken just prior to ending the session. Vital signs will be measured more frequently if there are 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. If medical attention is needed, the site physician (or physician on call) will provide further instruction or consult the Medical Monitor. If the participant experiences significant psychological distress which does not respond to processing with the facilitators, the C-SSRS may be administered. At the end of the Experimental Session (6+ hours after initial drug administration) the participant will complete the C-SSRS.

The facilitators will also record any AEs during the Experimental Session, and each AE will be rated mild, moderate, or severe (with mild defined as no limitation in normal daily activity, moderate as some limitation in normal daily activity and severe being unable to perform normal daily activity).

The facilitators will remain with the participant until:

- The physical and psychological effects of the session have substantially subsided.
- The participant is judged to be in a stable condition.
- The participant appears to have returned to Baseline mental status.

If the session was recorded to video by participant request, the facilitators will end recording when they have established that the participant has returned to Baseline function or is very close to doing so. They will complete all Source Records and will record any changes in the participant's health, such as AEs or SAEs.

Following the Experimental Session, the participant will be allowed to go home or to a nearby location. If they are not stable or the facilitators feel it is in their best interest, they may stay at the study site. Participants must not operate a vehicle for at least 24 hours after the initial MDMA dose administration. They should arrange a driver or a transportation service (such as a taxi) to go to their destination. Participants will be instructed not to use caffeine or nicotine for 6 hours after the initial MDMA dose administration.

6.1.4 Integrative Session (Visit 3)

On the morning after the Experimental Session, the participant will meet with the facilitators for a 1.5-hour integrative therapy session to discuss their experience, which will be recorded to video if the participant requests. The participant will complete the PANAS, AAQ-II, and C-SSRS just prior to beginning the Integrative Session. These measures may have been provided the evening prior, but participants should be instructed not to complete them until the morning of Visit 3.

The discussion during each Integrative Session may include:

- Processing of thoughts, feelings, or memories that arose during the Experimental Session.
- Addressing of goals set at the start of a previous session.
- Relation of the Experimental Session to anything the participant learned about MDMA-assisted psychotherapy research prior to the session, including information gleaned from the MDMA Therapy Training Program.

If the participant confronted unexpectedly intense or disturbing material during the Experimental Session, the facilitator(s) will provide means of continued contact throughout this day (Visit 3) as needed. If the participant requires, the facilitator(s) will provide additional contact and/or integrative therapy assistance beyond this visit, as needed.

Whenever possible the facilitators will follow the procedures for Integrative Session described in the Treatment Manual. Facilitators will also record changes in medication status and participant health, such as AEs or SAEs. Any reactions continuing outside of this period will be recorded and tracked as AEs.

The participant must have a pre-arranged ride from the study site to the place where they are residing, if the session ends earlier than 24 hours after their initial MDMA dose administration from the previous day. If this occurs and the participant has been unable to arrange transport, then the facilitator(s) will assist the participant in locating a ride to the appropriate location.

6.1.5 Telephone Contact

The facilitator(s) will contact the participant at 2, 7, and 60 days after the Experimental Session. This telephone contact will be for a brief check-in lasting 5 to 15 minutes, or as long as necessary to collect safety information and address any participant's concerns. The facilitator(s) will conduct the C-SSRS at the 2 and 7-day telephone calls only. Record any changes in the participant's medication status and health, including:

- AEs related to changes in psychiatric status.
- Clinically significant AEs requiring medical attention.
- AEs leading to withdrawal.
- SAEs.
- Concomitant medications review and adherence (only those related to AEs or SAEs will be collected at the 60-day telephone contact).

Additional contact or an additional Integrative Session can be scheduled at the request of the facilitator or participant. At the 60-day telephone contact, the investigator will collect the SCS, MBI-HSS, and PROQOL measurements before ensuring that all final safety information is complete, at which point the participant will terminate from the study.

6.2 Participant Numbering

Participant numbers will be assigned according to study site. The number assignments will be a unique eight-digit code placed with a leading “2”. Therefore, the first digit will always be “2”, the next three digits will reflect the associated site number, and the last four digits reflect the participant’s subject identifier. The codes will be generated per site and assigned to participants in ascending order upon enrollment. For example, the first participant number at site 001 will be 20010001.

6.3 Removal of Participants from the Study

Participants can withdraw consent or decide to discontinue treatment or participation in the study at any time without prejudice. The investigator can withdraw a participant if, in their clinical judgment, if it is in the best interest of the participant, if the participant experiences contraindications, or if the participant cannot comply with elements of the Experimental Session and related visits that are critical for safety. If the investigator withdraws a participant from the session, the investigator will explain the reason for withdrawal and have them replaced.

Participants will be clinically monitored after withdrawal, the cause of which will be recorded in the participant’s Source Records and eCRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE resolutions if deemed necessary by the investigator and/or site physician or sponsor Medical Monitor. If the participant terminates but does not withdraw consent, they should be followed for safety and proceed to follow-up visits as applicable and should also complete any remaining visits and/or follow-up telephone calls as indicated. If the participant withdraws consent, study records generated until the date consent is withdrawn will remain available for use by the sponsor and investigators.

6.4 Premature Discontinuation of the Study

The sponsor has the right to discontinue the protocol at any time. Each CI may decide to discontinue their respective site at any time, following consultation with the sponsor. If the protocol or site is prematurely terminated, the investigator will promptly inform participants and provide appropriate follow-up to participants, if necessary. If the protocol or site is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed.

7.0 Investigational Medicinal Product

7.1 MDMA Activity Related to Proposed Action

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce both defenses and fear of emotional injury while enhancing communication and capacity for introspection [52, 53]. Phase 2 studies of MDMA-assisted psychotherapy found reductions in PTSD symptoms when compared with inactive placebo or low-dose MDMA [13, 14, 16, 17, 42, 54-56]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased wellbeing, sociability, self-confidence, and extroversion [13, 14, 16, 17, 42, 54-56]. Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with Ecstasy (see for example versus [13]). An increase in positive mood, increased access to emotionally intense material, increased interpersonal trust and compassion for the self and others, and anxiolysis likely all contribute to

the therapeutic effects of MDMA. It is significant that anxiety is reduced without depressing the sensorium, and that participants/patients can still experience and reflect upon intense emotions. Increased interpersonal closeness may permit participants/patients to explore usually upsetting thoughts, memories, or feelings. Facilitated recall and unusual and potentially innovative shifts in thinking and perception may contribute to generating new perspectives about past or current thoughts, feelings, and experiences.

7.2 Description of Active Compounds

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

7.3 Encapsulation, Doses, Packaging and Labelling

Drug substance in bulk is sent from Onyx Pharmaceuticals, Inc., a current Good Manufacturing Practices (cGMP) drug substance manufacturer in the United Kingdom to Sharp Clinical Services, Inc., a Schedule 1 controlled substance-licensed cGMP drug product manufacturer in the United States. Sharp Clinical Services, Inc. will ensure that drug substance is compounded, encapsulated, packaged, labeled, and shipped to sites. Drug product will be placed in hydroxypropyl methylcellulose (HPMC) capsules and packaged in bottles as the final finished IMP.

This study employs an open-label design. Participants will receive an initial dose of 120 mg of MDMA and an optional supplemental dose of 40 mg or 60 mg MDMA (based on drug availability and clinical judgment) during one Experimental Session. The IMP is packaged in 40 mg and 60 mg MDMA (9 capsules) bulk presentation bottles. Bottles are labeled with a unique container number, protocol number, IMP name, lot number, sponsor name and a statement that the IMP is restricted to clinical trial use only. All labels will comply with US regulations.

Figure 2: Example of IMP Bottle Labels

Protocol#: MT2
C-I, IND# 63384
Container #: V
Lot #: V
Storage conditions: 15-25°C
Contains: 9 capsules of MDMA HCl 60 mg
Directions for use: Take by mouth and swallow with water
Caution: New Drug - Limited by Federal (or United States) law to investigation use
Multidisciplinary Association for Psychedelic Studies (MAPS)
1115 Mission Street, Santa Cruz, CA 95060

7.4 Accountability

Forms will be provided to track drug accountability and administration throughout the study. Drug accountability will be reviewed during routine monitoring visits.

7.5 Storage and Handling

MDMA is a Schedule 1 compound that will be stored and handled in compliance with relevant Federal and State regulations. In accordance with DEA requirements, the Schedule 1 License Holder will be responsible for storing and dispensing the MDMA. It will be stored in a metal cabinet or safe which has been inspected and approved by the DEA for this purpose. Only the Schedule 1 License Holder or authorized delegate will have access to the storage location. The research site will have an alarm system and will be locked whenever the Schedule 1 License Holder or authorized delegate is not present.

IMP will only be removed from storage once per participant at the time of the session. MDMA will be administered orally with a glass of water or electrolyte containing fluid. All doses administered will be recorded on the appropriate accountability logs.

Records pertaining to the use of Schedule 1 compounds will be maintained in accordance with relevant Federal and State Regulations. They will be kept separate from other records and maintained securely.

7.6 MDMA Stability

IMP is manufactured and packaged according to current Good Manufacturing Practices (cGMP). 6-month accelerated stability studies will be carried out along with ambient stability studies that will be ongoing for the duration of the study. All required Chemistry Manufacturing and Control (CMC) submissions will be made to the IND.

8.0 Risks in Study Participation

8.1 Non-drug Related Risks

8.1.1 Risks and Discomforts Associated with Medical Assessments

In preparation for MDMA-assisted psychotherapy sessions, blood draws and a full medical examination, including a physical examination, ECG with 1-minute rhythm strip, and laboratory tests, are required to establish eligibility for the study. Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Additional examinations or laboratory tests may take place to determine if candidates with specific conditions can safely enroll in the study. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

8.1.2 Risks and Discomforts Associated with Assessment of Measures, Psychotherapy Sessions, and Suicide Risk

Some study measures contain items that may provoke negative emotions. It is possible that completing these measures could be upsetting. During Screening and throughout study participation, participants will be asked to think about and discuss their thoughts and emotions, including thoughts about hurting or killing themselves. They may experience intense emotional responses as a result of recalling and speaking about this material if there is a pre-existing history of these thoughts. This is considered to be a rare risk in this participant population. Psychotherapy is conducted as part of this study, and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process. Because psychotherapy is an integral

part of the research study design, the potential distress arising from psychotherapy is unavoidable. Facilitators will provide emotional support to participants during any psychological distress.

The facilitators will minimize risks by carefully evaluating all possible participants to exclude those with suicide risk as determined through clinical interview and responses to the C-SSRS per Inclusion/Exclusion criteria specified in Sections 4.4.1 and 4.4.2.

A qualified individual will administer the C-SSRS according to Table 1: Time and Events (and as needed depending on clinical presentation of the participants) to monitor for development and intensity of suicidal ideation and/or behavior. The facilitator will implement the following plan to assess elevated or imminent suicide risk.

If the Since Last Visit C-SSRS reveals current serious Suicidal Ideation (scores of four or greater), indicating risk at the time of the assessment, or positive Suicidal Behavior, the participant will be referred for further management as described below:

1. If the participant has current suicidal ideation, but no specific plan to commit suicide (Suicidal Ideation Score=4), the facilitator administering the C-SSRS will ensure:
 - a. Participants are evaluated by the site physician to determine appropriate course of action and will discuss the findings with the participant.
 - b. Regular check-ins via telephone or in person will be continued until the participant has stabilized or a new course of action is taken based on changes in C-SSRS score and/or ongoing clinical assessment.
 - c. Notification of the sponsor within 24 hours of this event and provide a narrative for the AE for expedited reporting to FDA. Increases in suicidality will be captured as an AESI per Section 9.1.1 and evaluated for seriousness. SAEs will be reported per regulatory guidance.

2. If the participant has suicidal ideation, and a plan to commit suicide (Suicidal Ideation Score=5) or positive Suicidal Behavior, the facilitator administering the C-SSRS will ensure:
 - a. Participants are evaluated by the site physician to determine appropriate course of action.
 - b. If it is determined that the participant is at imminent risk of suicide, the CI or qualified staff member will do one of the following:
 - i. Escort the participant to the Emergency Department, or
 - ii. Escort the participant to an appropriate mental health services facility (e.g. hospital psychiatric unit), or
 - iii. Call 911 (emergency medical services) and ensure that the participant is transferred to the responding medical personnel.
 - c. If the participant will not comply and wishes to leave without consultation, call 911. Explain that the participant is in immediate danger of committing suicide. Provide a complete description of the participant and give any other needed details to ensure the participant's safety.
 - d. Notify appropriate members of the study team and sponsor representatives within 24 hours, provide a narrative for the AE for expedited reporting to the FDA.
 - e. The event will be collected as an AESI per Section 9.1.1 and seriousness will be evaluated. SAEs will be reported per regulatory guidance.

8.1.3 Risks Associated with Recorded Content

All psychotherapy sessions may be recorded to audio and video if the participant requests, for their own training purposes. There is a risk that participants may feel uncomfortable with having their sessions recorded. Therefore, they may request to stop the recording at any time.

The site may use audio-visual equipment previously provided by the sponsor (from other MAPS-sponsored studies) to record the sessions. However, the video should not be stored on the equipment and the audio-visual content should be copied to a storage device provided by the participant directly after the sessions. Therefore, since the recorded content will not be stored on MAPS equipment, it is not anticipated that there would be a security breach. In the case that an unforeseen security breach occurs, the participant will be notified, and all efforts will be made to minimize the dissemination of recorded content.

8.2 Risks of Receiving MDMA

Study procedures and eligibility criteria have been developed based on previous clinical trial data to exclude potential participants with pre-existing exclusionary medical conditions that would exacerbate risk. The facilitators and/or CI and/or site physician will be available via mobile phone throughout the study if any problem occurs when a participant is not at the site. In the event of a medical emergency or any other medical problem during the Experimental Session, the site physician will be immediately available by telephone, and based on assessment of the situation, they will make the decision to either evaluate the participant themselves at the site, have the facilitator call Emergency Medical Services to transport the participant to a hospital, or instruct the facilitator to take the participant to the hospital.

The risks of receiving MDMA are customized in this protocol for those that may occur in healthy populations. Further information on the risks associated with MDMA can be found in the IB. Risk mitigation procedures for this healthy population are described by risk category below. Risk Categories were determined by review of possible risks within the Risk Assessment and Categorization Tool (RACT).

8.2.1 High Level Risks

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

8.2.2 Medium Level Risks

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

8.2.2.1 Cardiovascular and Cerebrovascular Risks and Mitigation

MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes should last no more than 8 hours. 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 studies of MDMA-assisted psychotherapy detected a dose-dependent increase in systolic blood

pressure but not diastolic blood pressure. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing uncontrolled hypertension and monitoring blood pressure and pulse. Before and after IMP administration in the Experimental Session, the facilitator will monitor vital signs. In addition, the facilitator will attend to clinical signs and symptoms, such as chest pain, shortness of breath, neurological deficit or confusion or other potential indicators of end organ effects of hypertension that prompt additional vital sign measurements and possible interventions if appropriate. The facilitator will notify the site physician for evaluation if this occurs. If any participant has neurological deficits, as assessed by the site physician and whether or not they are associated with hypertensive crisis, they will be monitored, as described above, for rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, they will be given 0.4 mg of sublingual nitroglycerin every 5 minutes as needed for chest pain pending transport to the hospital. If evaluation at the hospital reveals a non-hemorrhagic stroke, there will be sufficient time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [57, 58].

If further evaluation at the hospital reveals that the participant has had an AMI, they will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in participants who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [59]. As the characterization of QT effects for the API is ongoing, QT interval may be evaluated in the event of hospitalization for management of cardiovascular or cerebrovascular event.

8.2.3 Low Level Risks

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

8.2.3.1 Psychological Risks and Mitigation

Mild anxiety and depressed mood are occasionally reported 1 to 3 days after MDMA administration [16, 42]. Psychological distress following MDMA administration could arise from the first indications of MDMA effects until the last effects have dissipated or even later. Anxiety or distress during the session may last for as little as several minutes or for as long as 5 hours or more. In addition, psychological distress could arise following the Experimental Session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting and have responded well to reassurance from the facilitator, with occasional use of benzodiazepines for anxiety. Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions may rarely occur in this participant population. This may be considered an element of the psychotherapeutic process.

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

- Excluding people who might be more vulnerable to it.
- The Preparatory Session of non-drug psychotherapy before the Experimental Session.
- Creating an atmosphere of trust during the Experimental Session.
- Close monitoring.
- Phone contact with participants during the week after the Experimental Session.
- Integrative Sessions.

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

If the participant is severely agitated, anxious, in danger of self-harm or suicide, or is experiencing any other severe psychological distress, at the end of a psychotherapy session a facilitator will remain with the participant for at least 2 more hours. During this time, the facilitator will employ affect management techniques, will talk with the participant to help them gain cognitive perspective of their experiences, and will help the participant implement self-soothing and stress inoculation techniques. Although not anticipated for this healthy population, if the participant remains severely anxious, agitated, in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of the 2-hour stabilization period, the site physician and facilitator will decide between the following options:

1. If severe distress occurs at the end of the Experimental Session, a psychiatric nurse, therapeutic assistant, physician, or facilitator will stay with the participant until the severe distress resolves. The facilitator will then meet with the participant daily until the period of destabilization has passed.
2. If the participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following the Experimental Session, a facilitator licensed to prescribe or the site physician may prescribe a benzodiazepine (e.g. lorazepam) and/or sleep aid (e.g., zolpidem). This medication will be captured on the Concomitant Medications eCRF. Residual symptoms will be addressed during the follow-up visits.
3. If a participant should become psychotic, or has other persistent severe symptoms that require more intensive monitoring and treatment, arrangements will be made to stabilize them or transfer them to the hospital, if necessary. Any participant who is hospitalized after a severe psychological reaction will be suspended from the protocol until after recovery or stabilization, at which time the investigator and/or site physician will carefully evaluate the participant's emotional status.

For those participants engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the participant's outside therapist will be involved in the management of any psychiatric complications. For those participants engaged in an ongoing psychotherapeutic relationship with the investigator or facilitators, the management of any psychiatric complications will be undertaken by them in their capacity as the participant's therapist.

8.2.3.2 Thermoregulatory Risks and Mitigation

MDMA administered in a controlled setting produces only a slight increase in body temperature [16]. Ambient temperature does not enhance or attenuate this slight elevation in humans. In data gathered from sponsor-supported Phase 2 studies, it was found that compared to placebo, a higher percentage of participants receiving MDMA had peak body temperatures greater than 1 degree Celsius (°C) above Baseline. However, there was no strong relationship between dose of MDMA and peak body temperature or between MDMA dose and elevation above threshold of 1°C above Baseline.

Ambient temperature will be kept at a comfortable level during the Experimental Session. If a participant's temperature rises more than 1°C or the participant states that they feel hot, attempts will be made to decrease body temperature and increase comfort by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5°C above Baseline despite these efforts, the site physician will be consulted for further evaluation and treatment.

8.2.3.3 Osmoregulatory Risk and Mitigation

MDMA administered in a controlled setting is not expected to have any risks of osmoregulatory changes. Participants will not be allowed to drink more than three liters of electrolyte-containing fluids over the course of the Experimental Session and fluid intake will be spread out appropriately during the session.

8.2.3.4 Genotoxicity Risk and Mitigation

To reduce the risk of metabolic activation and formation of nitroso-derivatives of MDMA due to potential interactions with nitrates or nitrites in food, participants are required to have fasted (no intake other than alcohol-free liquids and approved medications) for 10 hours prior to IMP administration at Experimental Session.

8.2.3.5 Reproductive and Developmental Risks

Risks posed by MDMA to pregnant participants are not known. One of two studies of Ecstasy users suggests that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth, while the other failed to find this association [60, 61] (see the IB).

To mitigate risk of reproductive or developmental exposure to the IMP, pregnant people will be excluded from participation in the study. Participants who are able to become pregnant must agree to use adequate birth control from the time of enrollment and through 10 days after the Experimental Session and have a negative pregnancy screen before receiving MDMA-assisted psychotherapy in the Experimental Session.

8.2.4 Minimal Risks

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

8.2.4.1 Common AEs

Common Adverse Events (AEs) are typically observed during IMP administration but are transient and diminish as the IMP is metabolized and excreted over the next 72 hours after dosing and are self-limiting. In healthy participants in the ongoing MT1 study, each participant receives MDMA and placebo in randomized order within the same week. Prevalence estimates of common AEs listed below include both conditions as the study is still blinded. Common AEs reported on the day of the Experimental Session (based on N=76) include:

- Jaw clenching or muscle tightness in the jaw (in about two-thirds of participants).
- Lack of appetite, muscle tension or headache (in about one-third of participants).
- Anxiety, perspiration or dizziness (in about one-fourth to one-fifth of participants).
- Sensitivity to cold, nausea, dry mouth, impaired gait/balance, nystagmus, fatigue, thirst, restlessness (between one-fifth and one-ninth of participants).
- Paresthesia, difficulty concentrating, heavy legs, low mood, drowsiness, weakness, insomnia, ruminations, diarrhea, need for more sleep, increased irritability or impaired judgement (in less than one-tenth of participants).

On the day after the Experimental Sessions, fatigue, headache, insomnia, jaw clenching or muscle tightness in the jaw, and muscle tension were reported by one-third to one-tenth of participants.

8.2.4.2 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [62]. However, these claims are based on studies that employed inappropriately high doses of MDMA utilized in animal studies and on human studies comparing the effects of repeated use of Ecstasy, often along with other drugs. By contrast, a recently published meta-analysis has taken careful steps to overcome methodological limitations in previous work and found only modest evidence of neurotoxicity [63]. The sponsor has carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. It does not appear that MDMA-assisted psychotherapy negatively impacts cognitive function.

8.2.4.3 Abuse Liability

Findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine. In sponsor-supported Phase 2 PTSD studies in 107 participants treated with MDMA-assisted psychotherapy in a controlled clinical setting, 29.9% (32 of 107) of participants had tried Ecstasy at least 6 months prior to enrollment, with U.S. samples demonstrating a higher prevalence of use than international studies.

Participants reported using Ecstasy an average of 2.3 (SD:1.43) times. Due to the known association of substance abuse and PTSD, this sample was likely not representative of the general healthy volunteer population but is congruent with the PTSD population. At long-term follow-up across studies, 8.7% of participants (8 of 92) reported “Ecstasy” use, and average times of use were 1.3 (SD:0.49) times. Six of these eight participants had used Ecstasy prior to study participation. Of these participants, most were attempting to recreate a therapeutic experience, and none indicated a desire to repeat this. In addition to self-report data, urine drug screens specific for MDMA were performed at random and 2, 6, and 12 months after the final Experimental Session during one study (MP2, N=12). All were negative, supporting the

observation that study participants did not seek out MDMA or Ecstasy after taking part in the study [7].

In addition to data on Ecstasy use at follow-up, AEs were reviewed across Phase 2 studies, the sponsor found an absence of clinically significant AEs supporting drug dependence, intentional drug misuse, and substance abuse, and a low rate (<2%) of secondary terms that reflect acute intoxication. Based on current information, it does not appear that MDMA-assisted psychotherapy demonstrates signals associated with known abuse liability patterns in a PTSD population when administered in a therapeutic setting under continuous observation in up to three single-dose sessions. Any abuse potential and diversion are further limited since the IMP is not supplied to the participant to take home and is administered in a restrictive setting. Each investigator responsible for dispensing or administration of the IMP will maintain current registration with authorities with oversight of controlled substances. IMP will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

9.0 Safety

9.1 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant which does not have a necessarily causal relationship with the treatment in question. An AE can, therefore, be any unfavorable or unintended sign (i.e. an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational treatment, whether considered to be related to the investigational treatment or not. This definition includes concurrent illnesses/ injuries and exacerbation of pre-existing conditions.

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

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

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

The severity of events reported on the “Adverse Events” eCRF will be determined by the CI or site physician as:

- Mild: no limitation in normal daily activity
- Moderate: some limitation in normal daily activity
- Severe: unable to perform normal daily activity

The relationship of each AE to the IMP will be determined via analysis and the opinion of the investigator will not be collected, with the exception of SAEs.

9.1.1 Adverse Events of Special Interest

In accordance with the Standards for Expedited Reporting International Conference on Harmonization (ICH) Topic E2A: Guidance for Industry and FDA Safety Reporting Requirements for INDs and Bioavailability/Bioequivalence (BA/BE) Studies, the sponsor will pay special attention to a subset of AEs involving cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias, including *Torsade de pointes*, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, syncope (non-postural), and seizures. The subset of AEs involving suicide risk under the following terms are also of special interest: suicides, suicide attempts, self-injurious behavior associated with suicidal ideation, and suicidal ideation judged to be serious or severe in the opinion of the investigator. These AEs will be marked in the eCRF as AESIs whether serious or non-serious.

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

- AESIs involving the terms of Behavioral addiction, Drug abuser, Substance abuser, Dependence, Intentional product misuse (including facilitation of product use outside of research setting), Overdose (accidental, intentional, or prescribed), or Drug diversion in cases that are related to MDMA or “Ecstasy” (material represented as MDMA) will be collected and coded as AESIs in the eCRF.
- Cases of noncompliance, protocol violations, participants lost to follow-up, and any other reasons why participants dropped out of the study will be assessed for presence of AESIs.
- Qualitative urine drug test data will be collected prior to the Experimental Session. Any positive findings that cannot be attributed to pre-approved concomitant medications or diet will be reviewed by the Medical Monitor to assess compliance with ongoing eligibility criteria and for presence of AESIs.

If an AESI is a Serious Adverse Event (SAE) or if it involves suicide risk, it should be reported to the sponsor with a narrative via the eCRF within 24 hours of the site’s awareness of the event.

9.1.2 Serious Adverse Events

In accordance with the Standards for Expedited Reporting ICH Topic E2A: Guidance for Industry and FDA Safety Reporting Requirements for INDs and BA/BE Studies, an SAE is defined as any untoward medical occurrence that at any dose:

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

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

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

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

9.2 Pregnancy

9.2.1 Definition of Childbearing Potential

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

9.2.2 Pregnancy Contraception Guidelines

Adequate birth control methods are required for participants of childbearing potential and include:

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Non-oral hormonal methods, including injected or implanted
- Oral, vaginal, or transdermal 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 birth control 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 birth control methods, contact the Medical Monitor.

9.2.3 Pregnancy Follow-up Requirements

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

This study includes a single Experimental Session with MDMA. Participants will undergo a pregnancy test at Screening, and again prior to drug administration during the Experimental Session. If the participant tests positive for pregnancy at Screening, they will not be enrolled in the study. If the participant tests positive for pregnancy prior to drug administration, they will not be eligible to proceed with the Experimental Session receiving the MDMA, and will be discontinued from the study.

In the event of a pregnancy after the Experimental Session, the participant may continue with follow-up and Study Termination procedures. The investigator will collect follow-up information on the participant and neonate and forward to the sponsor until the outcome of the pregnancy, which will be reported on an optional Pregnancy eCRF. Any termination, elective or spontaneous, will be reported. Abnormal pregnancy outcomes, such as spontaneous abortion, fetal death, stillbirth, congenital abnormalities, or ectopic pregnancy, will be reported as SAEs.

10.0 Concomitant Medications

The site will record concomitant medications during Screening. The participant will be asked about any changes in medication at each visit and during the follow-up contacts. 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 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.

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.

All medications, herbal and dietary 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 site physician and Medical Monitor judgment.

10.1 Prohibited Medications and Tapering Instructions

If the prospective participant is being treated with prohibited medications at screening for a non-excluded condition, they 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. Prohibited medications will then be tapered in an appropriate fashion to avoid withdrawal effects.

Participants must be willing to taper off of prohibited medications prior to Visit 1 and refrain from use until 40 hours (five half-lives of MDMA) after the Experimental Session. Prohibited medications will be tapered for at least five half-lives of the drug or active metabolites prior to the Experimental Session to avoid the possibility of interactions.

Participants must agree that, for approximately 1 week preceding the first Experimental Session, they:

- Will refrain from taking any herbal or dietary supplement (except with prior approval of the research team).
- Will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen) unless with prior approval of the research team.
- With the permission of their physician, will not take any prescription medications (with the exception of contraception medications, thyroid hormones, or other medications approved by the research team).

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

11.0 Clinical Laboratory Assessments

The CI or site physician will examine the laboratory assessments gathered in screening to assess participant eligibility. The investigator or site physician will use a list of normal ranges to decide whether participants are eligible for the protocol and will indicate justification for admitting participants with abnormal values. The following laboratory assessments will be performed as a part of screening:

- Serum electrolytes and comprehensive metabolic profile
 - Alanine Aminotransferase (ALT/SGPT)
 - Albumin:globulin (A:G) ratio
 - Albumin, serum
 - Alkaline phosphatase, serum
 - Aspartate Aminotransferase (AST/SGOT)
 - Bilirubin, total
 - BUN:creatinine ratio
 - Calcium, serum
 - Carbon dioxide
 - Chloride, serum
 - Creatinine, serum
 - Globulin, total
 - Glucose, serum
 - Potassium, serum
 - Protein, total, serum
 - Sodium, serum
- CBC
 - Hematocrit
 - Hemoglobin
 - Mean Corpuscular Volume (MCV)
 - MCH

- MCHC
- Red Cell Distribution Width (RDW)
- Percentage and absolute differential counts
- Red blood cell count (RBC)
- White blood cell count
- Urinalysis
 - Color
 - Appearance
 - Specific gravity
 - pH
 - Protein
 - Glucose
 - Ketones
 - Occult blood
 - Leukocyte esterase
 - Nitrite
 - Bilirubin
 - Urobilinogen
- Thyroid function
 - Thyroid Stimulating Hormones (TSH) high sensitivity
 - If TSH is abnormal, Free T4
- HIV serology (results should be kept confidential, and appropriate referral for counseling will be made, if necessary)

These laboratory assessments will be performed by a laboratory of the participant's choosing, by the study's central laboratory (e.g. LabCorp, TriCore), or by another qualified laboratory. The results may be provided by the participant to the site for review by the site physician. Individuals who have prior results for the above tests dated within 12 weeks of screening will be permitted to use these results rather than undergoing a new set of screening labs.

The urine drug screen and pregnancy test must be performed at the study site.

Laboratory records will be kept with the participant's Source Records but will not be captured in the electronic Case Report Form (eCRF). Abnormal laboratory values, however, will be recorded in the medical history portion of the participants Source Record and eCRFs, if clinically significant.

12.0 Study Monitoring, Auditing, and Documentation

Investigators and site staff will be trained prior to the start of the protocol. The clinical study sites will be monitored as appropriate for the rate of enrollment via site visits and telephone calls to the CI by representatives of the sponsor. During monitoring visits, source data verification may be performed to ensure compliance, including accurate and complete recording of data on eCRFs, Source Records, and drug accountability records. Monitoring/auditing procedures of the sponsor will be followed in order to both comply with good clinical practice (GCP) guidelines and ensure validity of the study data.

The sponsor will review the study documentation used for planning, conducting and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes at a minimum: The Investigator's Brochure, the Study Protocol, the eCRF database, and the ICF.

During or after the clinical protocol, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all Source Records, eCRFs, and other protocol documentation for on-site audit or inspection.

13.0 Data Analysis

In general, nominal variables will be described in terms of frequencies and percentages. Ordinal and non-normal continuous variables will be described using sample median and range, and approximately normal variables will be described using sample mean and standard deviations. All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant

Descriptive statistics will be calculated for all measures, demographics, and Baseline characteristics. The primary and exploratory outcome measure scores (for SCS, PANAS, AAQ-II, PROQOL, and MBI-HSS) will be evaluated by performing a mixed model repeated measures analysis (MMRM) at an alpha level of 0.05, with time of administration as repeated measure. There will be no between-subjects or groups factors.

Effect size (Cohen's *d*) will be determined by employing a one group pretest-posttest design (RM), where the mean difference in the pretest-posttest is divided by the standard deviation of raw scores [64].

Safety measures will be presented by descriptive statistics for Baseline C-SSRS scores, blood pressure, pulse, and temperature values. For the Experimental Session, an MMRM analysis will evaluate vital sign values. AEs will be collected according to the Time and Events table and presented as frequency tables as prior to MDMA dose, day of Experimental Session, 2 and 7 days following the Experimental Session, and any other time outside of the stated windows.

Suicidal ideation and behavior will be summarized according to suggestions made in the Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide [65]. A positive response for suicidal ideation is counted when a participant answers "yes" to any one of the five suicidal ideation questions (Categories 1 to 5) on the C-SSRS, i.e. a score > 0 for suicidal ideation score. Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a participant answers "yes" to any one of the five suicidal behavior questions (Categories 6 to 10) on the C-SSRS. The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated by visit.

The study will include a planned interim analysis by internal review after 50% of participants are treated to assess ongoing safety. The primary efficacy analysis will be conducted after all participants complete the study, but interim analyses may be performed prior. Post-hoc exploratory analyses not identified in this protocol or the Statistical Analysis Plan may be performed to further examine the study data.

13.1 Statistical Power

The proposed study is a pilot investigation intended to explore the safety and psychological effects of open-label manualized MDMA-assisted psychotherapy. Due to the exploratory nature, this pilot study is not powered to detect any particular effect. Effect size estimates that will be generated from this study will be used for statistical power calculations for future studies on professional burnout and quality of life experienced by treatment providers learning to deliver MDMA-assisted psychotherapy. Data generated in these areas has the potential to improve the

quality of care that PTSD patients will ultimately receive. This is an imminent concern that has broad impact on the healthcare system.

14.0 Ethics

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Guidelines for Good Clinical Practice, with applicable national and local regulations. The protocol and the ICF must be reviewed and approved by a properly constituted IRB and FDA before study start. Signed and dated documentation of IRB and FDA approvals must be provided to the sponsor. Prior to study start, the CIs are required to sign a protocol 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.

15.0 Informed Consent

Qualified site staff are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the participant into the trial. Information about events during the MDMA-assisted session must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the study, including of the Experimental Session and the participant's legal rights, the ICF should specify that access to original medical records and processing of coded personal information is authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable, local regulations. The participant should have the opportunity to inquire about details of the Experimental Session and to consider participation.

The ICF must be signed and dated by the participant and countersigned by qualified site staff providing the ICF review. The site staff will provide a copy of the signed ICF to the participant and maintain the original in the investigative site file. The written ICF should be revised along with any other written information to be provided to participants whenever important new information becomes available that may be relevant to the participant's consent. Any revised, written ICF or other 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 in the MDMA-assisted session. The communication of this information should be documented.

Because this research study is an optional element open only to those who are enrolled in or have completed the MDMA Therapy Training Program, the sponsor may have access to the names of participants as enrollees in the training program. However, only the participant numbers and participant identification codes will be recorded in the eCRF. Written consent to take part in the MDMA-assisted session includes giving the investigators permission to view the participant's recent 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.

Participants can withdraw consent for participation in the protocol at any time without prejudice. If a participant withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization or equivalent form, MAPS will have full access to the participant's source records, including termination visit information. If a participant revokes only the HIPAA authorization, MAPS will have full access to all of the participant's source records prior to the date and time of revocation.

16.0 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 participant should prevent the dissemination of confidential data. Except for the Screening Log, 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 subject identifier. Participants will sign the ICF for the release of information upon consent to permit screening for protocol enrollment. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data.

Researchers, other than the investigators and site 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 a 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.

If a participant requests that their session(s) be recorded to audio and video for their own training purposes, the site may use equipment on site that was previously provided by MAPS for other MAPS-sponsored studies. However, the recorded content should not be saved within the equipment and should be copied to an external storage device (such as an external hard drive or flash drive) provided by the participant immediately after the session(s). Neither MAPS, nor its affiliates, will have access to the recorded content. Therefore, since the recorded content will not be stored on MAPS equipment, it is not anticipated that there would be a security or confidentiality breach. In the case of an identified security or confidentiality breach, the participant will be notified, and all efforts will be made to minimize the dissemination of recorded content.

Clinical trial data will be hosted on an electronic data capture (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 an electronic Participant Reported Outcome (ePRO) feature, which transmits directly into the eCRF database. 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. In the event of technical difficulties or other unforeseeable issues, the self-report questionnaire data may be entered directly on its associated form and kept with the participant's source record files.

Medical records, consent forms, and source data resulting from the study which identify the participant may be looked at and/or copied for research or regulatory purposes. These records may be observed by:

- The sponsor, affiliated companies, and the people they hire.
- Researchers who cooperate with the sponsor to conduct further research.

- The FDA and similar regulatory agencies in other countries.
- Governmental agencies in other countries.
- The IRB.

17.0 Costs to Participants

The sponsor will cover costs of assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of a participant's condition that are unrelated to the research study or any unrelated procedures will not be covered by the sponsor. Participants will not receive monetary compensation for taking part in the study.

18.0 Treatment and Compensation for Study Related Injury

Treatment of a study-related emergency would first be billed to a participant's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a participant's health insurance. Some study-related emergencies can be treated by the investigators, as described under Section 7.0 Risks in Study Participation. If the site physician cannot treat a study-related emergency, then there are contingency plans for the transport of participants to the nearest hospital.

19.0 Record Retention

Investigators must retain all study records required by MAPS and the applicable regulations in a secure and safe facility. The CI must consult a MAPS representative 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. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

20.0 References

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