Protocol and Synopsis MT1
IND #063384

Original Protocol Version 1: 19 June 2009
Amendment 1 Version 1: 16 September 2009
Amendment 2 Version 1: 02 December 2009
Amendment 3 Version 1: 18 April 2016
Amendment 4 Version 1: 19 February 2019
Amendment 5 Version 1: 05 February 2020
Amendment 5 Version 2: 08 April 2020

A Phase 1 Placebo-Controlled, Double-Blind, Multi-Site Crossover Study to Assess
Psychological Effects of MDMA when Administered to Healthy Volunteers

SPONSOR Multidisciplinary Association for Psychedelic Studies (MAPS)
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Santa Cruz, CA 95060

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Medical Monitor

USE In conjunction with relevant regulatory and ethical guidance

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Title

A Phase 1 Placebo-Controlled, Double-Blind, Multi-Site Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers

Study Code

MT1

Sponsor

Multidisciplinary Association for Psychedelic Studies (MAPS)
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Investigators

Multi-site

Medical Monitors

Alia Lilienstein, M.D.
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Study Description

This Phase 1, multi-site study will collect safety and quantitative data on mood, psychological symptoms, personality traits, and interpersonal closeness in up to 120 participants learning to conduct 3,4-methylenedioxymethamine (MDMA)-assisted psychotherapy or MDMA research through the MDMA Therapy Training Program.

The study will be conducted by co-facilitator teams approved by the sponsor. The investigators will conduct two Experimental Sessions in approved treatment facilities. Participants will undergo a 1.5-hour Preparatory Session with the investigators prior to the first Experimental Session to prepare the participants. Participants will be randomly assigned to the condition of either placebo or MDMA during the first day-long Experimental Session (Visit 2). For the second Experimental Session (Visit 4), at least 48 hours and no more than 3 months after the first Experimental Session, participants will cross over to the alternate condition. During each blinded Experimental Session, participants will receive an initial dose of either placebo or 125 mg MDMA (as the hydrochloride salt or “HCl”, referred to as MDMA throughout), followed by an optional supplemental half-dose 1.5 to 2 hours later.

Following each Experimental Session, the participant will stay overnight at the study site or appropriate location approved by site team. Each participant will have a 1.5-hour integrative psychotherapy session on the day after their Experimental Sessions (Visits 3 and 5) to address thoughts and feelings that come up during the Experimental Sessions. The investigators will contact the participant by phone for safety follow-up on the day after each of the Integrative Sessions, then every other day for the next 12 days. If the second Experimental Session starts at
any time within the 12-day safety follow-up period, no additional safety follow-up is required from the first Experimental Session.

The investigators will then contact the participant by phone at 1 month and 2 months after the second Experimental Session to complete study measures, monitor safety, and help participants understand and integrate their experience.

This study will prospectively examine mood in healthy participants before and after drug administration to gain an understanding of the acute effects of the drug vs. placebo in a therapeutic setting. Effects of MDMA-assisted psychotherapy on personality traits in healthy volunteers will also be assessed. Participants who are learning how to conduct MDMA-assisted psychotherapy or MDMA research through the MDMA Therapy Training Program will have the opportunity to gain first-hand experience within this study.

Dose Selection

This study will compare the effects of psychotherapy sessions assisted with either placebo or an active dose of MDMA. The active dose will be 125 mg MDMA followed 1.5 to 2 hours later by an optional 62.5 mg supplemental dose. The same dosing regimen will be followed for placebo to maintain the study blind.

The MDMA dose used in this study has been used in previous MAPS-sponsored studies. The initial active dose is expected to produce all 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.

Protocol Objectives

The overall objective of this study is to collect data regarding the psychological effects of manualized MDMA-assisted psychotherapy in healthy volunteers, assess safety, and to expand the knowledge of trainees learning to conduct MDMA-assisted psychotherapy research.

Primary Objective

To assess changes in current mood state as measured by Profile of Mood States-Bi Polar Version (POMS-Bi) on the day of the Preparatory Session, at the end of each Experimental Session (6+ hours after drug administration), at the beginning of each Integrative Session, and at the 2-month Follow-up.

Exploratory Objectives

The protocol will meet the following exploratory objectives:

- To assess changes in interpersonal closeness from Baseline on the day of the Preparatory Session, Experimental Sessions, and Integrative Sessions.
- To assess personality traits at Baseline and 2 months after the last Integrative Session using the Neuroticism-Extroversion-Openness Personality Inventory (NEO).
Safety Objectives

The overall safety objective is to monitor and assure the safety of participants during each Experimental Session and throughout the clinical protocol by monitoring physiological drug effects, psychological symptoms, suicidal thoughts or behavior, spontaneously reported reactions (SRRs), AEs (Adverse Events), and SAEs (Serious Adverse Events) as follows:

- Suicidal ideation and behavior will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline, at the Preparatory Session, twice during each Experimental Session, at each Integrative Session on the day following an Experimental Session, during the telephone contact 1 day after the Integrative Sessions and every other day for the next 12 days, and 1 month and 2 months after the first Experimental Session. If the second Experimental Session starts at any time within the 12-day safety follow-up period, no additional safety follow-up C-SSRS administrations are required from the first Experimental Session.

- Subjective Units of Distress (SUD) scores and vital signs including blood pressure, heart rate, and body temperature will be measured several times throughout each Experimental Session. Comparisons will be made for vital signs by condition.

- Spontaneously reported reactions (SRRs) will be collected during and 2 days after each Experimental Session. This time window was selected based on MDMA’s elimination half-life of 7 to 9 hours, and most reactions are expected to cease within 2 days post-drug in a healthy volunteer population. Any reactions persisting beyond the 2-day window will be recorded and tracked as AEs.

- The Brief Symptoms Inventory (BSI) will be used to assess clinical and psychological symptoms at the Preparatory Visit, prior to and near the end of the Experimental Sessions, at the Integrative Sessions, and at the last Telephone Follow-Up Visit.

- AEs and Serious Adverse Events (SAEs) will be collected from enrollment through Study Termination. This includes any clinically significant AEs requiring medical attention, any AEs leading to withdrawal from the protocol, and any 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.

Additional administrations of the C-SSRS will be performed at any time during the study if a participant is experiencing psychological distress. If any Since Last Visit C-SSRS reveals an increase in scores past the Baseline assessment (Visit 1 since last visit C-SSRS), the event will be collected as an Adverse Event and seriousness will be evaluated. Sites will be required to notify the Clinical Trial Leader (CTL) and the Medical Monitor soon as possible.

Primary Outcome Measure

POMS-Bi

Exploratory Outcome Measures

Measure of State Interpersonal Closeness (IPC) and Neuroticism-Extroversion-Openness Personality Inventory (NEO)
Safety Measures

Columbia Suicide Severity Rating Scale (C-SSRS), Vital Signs, Subjective Units of Distress (SUD), Brief Symptoms Inventory (BSI), Adverse Events (AE), and Spontaneously Reported Reactions

Process Measure

Belief of Condition Assignment

Recruitment and Subject Population

The investigators will recruit persons aged 21 or older who are 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, doctorate-level professionals, graduate students in a relevant field, individuals practicing a related healing profession (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 limitations on concomitant medications and to complete study procedures. If the participant is of childbearing potential, they must have a negative pregnancy test and agree to use an effective form of birth control. All participants must be proficient in reading and speaking English.

Study Procedures

After giving written informed consent, candidates will be screened for eligibility, and up to 120 participants meeting study criteria will be enrolled. 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 either the first or the second Experimental Session, with investigator and participant remaining blind to order of condition assignment. Safety follow-up telephone calls will be made to the participant the day after each Integrative Session, then every other day for the next 12 days. If the second Experimental Session starts at any time within the 12-day safety follow-up period, no additional safety follow-up is required from the first Experimental Session. The investigators will then contact the participant by phone at 1 month and 2 months after their last Experimental Session. Preparatory, Experimental, and Integrative Sessions may be video-recorded so the participant can have a copy for their records, if they request. The participant may wish to review the recordings as a means of observing and retaining information to support their own reflection on the MDMA-assisted psychotherapy experience.

Prior to beginning the Preparatory Session, the participant will complete the POMS-Bi, IPC, NEO, C-SSRS, and BSI. The participant will then undergo a 1.5-hour Preparatory Session with the co-facilitator team prior to the first Experimental Session. The facilitators will assess General Wellbeing, after which the rest of the session will be used to prepare the participant for the Experimental Sessions in accordance with the Treatment Manual. Experimental Session 1 (Visit 2) will occur 1 day after the Preparatory Session and Experimental Session 2 (Visit 4) will occur at least 48 hours and no more than 3 months after Experimental Session 1. The participant will complete the C-SSRS and BSI 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 and is followed by an overnight stay at the study site or appropriate location approved by site team. The participant will complete the POMS-Bi, IPC, C-SSRS, and BSI at the end of the Experimental Session (6+ hours after drug administration).

On the morning after each 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 POMS-Bi, IPC, C-SSRS, and BSI just prior to beginning the Integrative Session, at which point both the participant and investigators will indicate their belief of condition assignment. The day after each Integrative Session (Visit 3 and Visit 5), one or both of the study facilitators will contact the participant. The telephone contact will be for a brief check-in lasting between 5 to 15 minutes or as long as necessary to address any participant concerns, assess wellbeing, conduct measures, and address any important changes. The investigators will then contact the participant by phone for safety follow-up every other day for the next 12 days. If the second Experimental Session starts at any time within the 12-day safety follow-up period, no additional safety follow-up is required from the first Experimental Session.

The investigator will also contact the participant 1 month and 2 months after Experimental Session 2 (Visit 4) to conduct outcome measures and follow-up on any adverse events.

**Statistical Analysis**

Descriptive statistics will be calculated for all measures. The primary outcome measure of the six POMS-Bi subscale scores will be analyzed by classic methods for crossover studies. The Primary Endpoint analysis will employ a paired t-test at an alpha level of 0.05. A Bonferroni correction will be applied to preserve the overall Type 1 error rate for the 6 hypothesis tests. Exploratory analyses include a repeated measures Analysis of Variance (ANOVA) of interpersonal closeness and a paired samples t-test of NEO scores at Baseline and 2-month Follow-up. Safety analyses include change from Baseline BSI and C-SSRS scores, blood pressure, pulse, and temperature values at specified time points. AEs will be collected according to the Time and Events table and presented as frequency tables.
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<th>Definition</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
</tr>
<tr>
<td>AE(s)</td>
<td>Adverse Event(s)</td>
</tr>
<tr>
<td>ALT/SGPT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>BA/BE</td>
<td>Bioavailability/Bioequivalence</td>
</tr>
<tr>
<td>BSI</td>
<td>Brief Symptoms Inventory</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
</tr>
<tr>
<td>CI</td>
<td>Clinical Investigator</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>DEA</td>
<td>Drug Enforcement Administration</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>DMF</td>
<td>Drug Master File</td>
</tr>
<tr>
<td>DSM-V</td>
<td>Diagnostic and Statistical Manual of Mental Disorders - V</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloride</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
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<tr>
<td>IB</td>
<td>Investigator Brochure</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IPC</td>
<td>Interpersonal Closeness Measure</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
</tr>
<tr>
<td>IUS</td>
<td>Intrauterine hormone-releasing system</td>
</tr>
<tr>
<td>LSD</td>
<td>d-lysergic acid diethylamide</td>
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<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MAPS</td>
<td>Multidisciplinary Association for Psychedelic Studies</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean Corpuscular Hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean Corpuscular Hemoglobin Concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean Corpuscular Volume</td>
</tr>
<tr>
<td>MDMA</td>
<td>3,4-methylenedioxymethamphetamine</td>
</tr>
<tr>
<td>mmHg</td>
<td>Milligrams of Mercury</td>
</tr>
<tr>
<td>MPBC</td>
<td>MAPS Public Benefit Corporation</td>
</tr>
<tr>
<td>NEO</td>
<td>Neuroticism-Extroversion-Openness Personality Inventory</td>
</tr>
<tr>
<td>POMS-Bi</td>
<td>Profile of Mood States - Bi Polar Version</td>
</tr>
<tr>
<td>PTCA</td>
<td>Percutaneous Transluminal Coronary Angioplasty</td>
</tr>
<tr>
<td>PTSD</td>
<td>Posttraumatic Stress Disorder</td>
</tr>
<tr>
<td>RACT</td>
<td>Risk Assessment and Categorization Tool</td>
</tr>
<tr>
<td>RBC</td>
<td>Red Blood Cell Count</td>
</tr>
<tr>
<td>RDW</td>
<td>Red Cell Distribution Width</td>
</tr>
<tr>
<td>SAE(s)</td>
<td>Serious Adverse Event(s)</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>SRR(s)</td>
<td>Spontaneously reported reaction(s)</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin-norepinephrine Reuptake Inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>SUD</td>
<td>Subjective Units of Distress</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormones</td>
</tr>
<tr>
<td>U.S.</td>
<td>United States of America</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell Count</td>
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</table>
1.0 Introduction, Background, and Rationale

1.1 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval as a clinical trial sponsor for the prescription use of 3,4-methylenedioxyamphetamine (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 United States of America (U.S.) Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for MDMA-assisted psychotherapy for treatment of PTSD in 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.
This protocol is for a Phase 1 study for up to 120 healthy volunteers. The information gathered during this study may help the scientific and medical communities not only to better understand the psychological effects catalyzed by MDMA-assisted psychotherapy, but also how those effects can more effectively be put to work treating PTSD patients in a therapeutic context. Additionally, safety data will be gathered by the investigators to further support the safety profile of this combined treatment.

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 [10-12]. This Phase 1 study will examine mood and symptoms both during the duration of the drug effects and at a number of various time points beyond 8 hours, all within a therapeutic setting. More stable human characteristics, such as personality, have not yet been assessed in healthy volunteers both before and after MDMA-assisted psychotherapy. However, personality factors have been assessed in participants with PTSD in the sponsor’s recently completed Phase 2 trial of MDMA-assisted psychotherapy in people with PTSD, with some evidence of changes as a result of exposure to MDMA-assisted psychotherapy. The same personality measure will be used in this Phase 1 study.

Enrollment in this protocol is limited to people who meet the inclusion criteria without meeting any of the exclusion criteria and who are engaged in learning to conduct MDMA-assisted psychotherapy studies. In addition to measuring psychological effects of MDMA-assisted psychotherapy, this protocol will provide trainees with a learning opportunity, insight into the experience of MDMA in a therapeutic context, and a better understanding of the techniques taught in the MDMA Therapy Training Program.

The MDMA-assisted session will not be offered until appropriate Institutional Review Board (IRB) approval of the protocol and the informed consent document have been obtained. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and other authorities, if applicable, will be informed of protocol amendments in accordance with local legal requirements.

Experimental sessions will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines, and applicable standard operating procedures. The session will be conducted under a protocol reviewed and approved by an IRB. Psychotherapy sessions will be conducted by qualified persons according to the most recent Treatment Manual. The rights and welfare of the participants will be respected. The investigators conducting the trial do not find the hazards to outweigh the potential benefits. Each participant will give written informed consent before any protocol-related tests or evaluations are performed.

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.

1.2 Background Information

1.2.1 Supporting Information

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 [13, 14], 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 [11, 12, 15, 16]. Assessments of mood occurred in medical or neuroscience laboratory settings often involving cognitive tasks, imaging or physiological assessment, and assessment of mood 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 [10, 11]. 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. 17, 18-20].

Some researchers have specifically assessed the acute effects of MDMA with the Profile of Mood States measure [12, 13, 16]. Of these studies, only one has assessed mood the morning after nocturnally administered MDMA [12]. A few investigators have examined sub-acute effects, but generally as self-reported reactions and not effects on mood [11, 21]. To date, there are no trials that have investigated the effects of mood approximately 24 hours after MDMA administration.

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 a nondirective but focused manner, with intermittent support from the facilitators. 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.

Personality measures have not been used in clinical trials of MDMA in healthy volunteers. These measures are intended to measure cross-situationally stable facets of personality, such as degree of extroversion or neuroticism. There is some evidence of age-related changes in at least some personality factors [22, 23], and preliminary evidence of changes in the NEO in people with PTSD after MDMA administration in a Phase 2 clinical trial. Hence, it is possible that MDMA administration could have an effect on personality scores in healthy volunteers.

Narrative reports of the effects of MDMA, including reports from therapeutic use, describe increased empathy and acceptance for self and others, as well as increased feelings of closeness toward others [18, 19, 24]. Changes in empathy, interpersonal closeness, and acceptance may each play a role in the therapeutic effects of MDMA. Only three human trials of MDMA have attempted to directly assess self-reported empathy or sociability, in all cases through a subset of items on surveys of subjective effects [21, 25, 26], with two of three finding an increase in sociability or closeness to others. While there are a number of instruments measuring trait empathy or compassion [27], few assess state empathy. A study in healthy volunteers demonstrating the prosocial effects of MDMA through a less direct measure, as through a nonverbal measure of perceived social distance, may be able to discover the presence and of changes in interpersonal closeness experienced after MDMA ingestion.
This exploratory protocol will use the Profile of Mood States-Bi Polar Version (POMS-Bi), an established measure of current mood states employed in human MDMA trials [12, 13, 16], as well as the Neuroticism Extroversion Openness (NEO) Personality Inventory (a widely used personality measure), to examine potential changes in these areas. The protocol will examine mood in healthy participants 1 day before drug administration and as drug effects are waning during the Experimental Session, as well as during the days after the session.

Enrollment in this study will be limited to a maximum of 120 volunteers learning to conduct MDMA-assisted psychotherapy or MDMA research through the MDMA Therapy Training Program. 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 [28]. 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 [29].

Personal experience is considered beneficial by practitioners of psychotherapeutic methods such as hypnosis and psychoanalysis, and by teachers of meditation and yoga. 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 within a controlled protocol such as this one.

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 1970s, 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 administered 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 [30-32]. 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 [33] 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., 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 [34].

1.2.2 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 (as the hydrochloride salt or “HCl”, referred to as MDMA throughout) to be used in this protocol are identical to those in use in the studies of MDMA-assisted psychotherapy research completed in the U.S., Switzerland, Canada, and Israel. Previous researchers have also used doses within this range \[11, 15, 21, 35, 36\].

A limited number of human trials of MDMA have attempted to assess empathy or interpersonal closeness, an effect of potential relevance within a therapeutic setting. When given in a different context, it is probable that MDMA will produce different effects. A psychotherapeutic context possesses several features that differentiate it from a clinical laboratory setting, including a focus on introspection and relatively unstructured interactions with the investigators. This Phase 1 study is designed to examine the specific effects of MDMA on interpersonal closeness during the acute phases of drug administration when administered in a psychotherapeutic setting in healthy volunteers. Interpersonal closeness will also be assessed a day before and a day after administration.

### 1.3 Protocol Purpose

One purpose of the study is to collect quantitative data on mood, psychological symptoms, personality traits, and self-reported interpersonal closeness in healthy volunteers after placebo and MDMA administration within a therapeutic setting through use of established measures of mood state, symptoms, and personality. This exploratory study will permit an understanding of the acute effects of the drug in a specific and relevant setting for use in therapy and will include comparison with placebo. It may also permit meta-analytic comparison of personality assessment between people with PTSD and healthy volunteers before and after MDMA administration. This is a multi-site protocol.

This Phase 1 study will use a novel measure developed by Lisa Jerome, Ph.D., to examine the specific effects of MDMA on interpersonal closeness during the acute phase of the drug effects when administered in a psychotherapeutic setting in healthy volunteers. Interpersonal closeness will also be assessed on the day after drug administration.

Currently, the MDMA Therapy Training Program is teaching therapists how to conduct MDMA-assisted psychotherapy based on the Treatment Manual for MDMA-assisted psychotherapy. This training is expected to be active throughout the Phase 3 program. 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 without any prior personal experience with MDMA, and MAPS will not require therapists conducting studies to have such experiences. This protocol will provide trainees who are engaged in learning to conduct MDMA-assisted psychotherapy or MDMA research through the MDMA Therapy Training Program with the opportunity to gain first-hand experience of the effects of MDMA administered in a therapeutic setting, which is likely to make a significant contribution to a therapist’s effectiveness in conducting clinical trials with MDMA, and to offer valuable contributions to the safety profile of MDMA in healthy volunteers.

### 2.0 Protocol Objectives

The objectives of the protocol are to collect data regarding the psychological effects of MDMA in healthy volunteers through a randomized, double-blind, placebo-controlled crossover design, assess safety, and to expand the knowledge of trainees learning to conduct MDMA-assisted psychotherapy research.
2.1 Primary Objective

The protocol will meet the following primary objective:

- To assess changes in current mood state as measured by POMS-Bi on the day of the Preparatory Session, at the end of each Experimental Session (6+ hours after drug administration), at the beginning of each Integrative Session, and at the 2-month Follow-up.

2.2 Exploratory Objectives

The protocol will meet the following exploratory objectives:

- To assess changes in interpersonal closeness from Baseline on the day of the Preparatory Session, Experimental Sessions, and Integrative Sessions.
- To assess personality traits at Baseline and 2 months after the last Integrative Session using the NEO Personality Inventory.

2.3 Safety Objectives

The overall safety objective is to monitor and assure the safety of participants during each Experimental Session and throughout the clinical protocol by monitoring physiological drug effects, psychological symptoms, suicidal thoughts or behavior, spontaneously reported reactions (SRRs), AEs, and SAEs as follows:

- Suicidal ideation and behavior will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline, at the Preparatory Session, twice during each Experimental Session, at each Integrative Session on the day following an Experimental Session, during the telephone contact 1 day after the Integrative Sessions then every other day for the next 12 days, and 1 month and 2 months after the first Experimental Session. If the second Experimental Session starts at any time within the 12-day safety follow-up period, no additional safety follow-up C-SSRS administrations are required from the first Experimental Session.
- SUD and vital signs (blood pressure, heart rate, and temperature) will be measured several times throughout each Experimental Session. Comparisons will be made for vital signs by condition.
- Spontaneously reported reactions (SRRs) will be collected during and 2 days after each Experimental Session. This time window was selected based on MDMA’s elimination half-life of 7 to 9 hours, and most reactions are expected to cease within 2 days post-drug in a healthy volunteer population. Any reactions persisting beyond the 2-day window will be recorded and tracked as AEs.
- BSI will be used to assess clinical and psychological symptoms at the Preparatory Visit, prior to and near the end of the Experimental Session, at the Integrative Sessions, and at the 2-month Follow-up.
- AEs and SAEs will be collected from enrollment through Study Termination. This includes any clinically significant AEs requiring medical attention, any AEs leading to withdrawal from the protocol, and any 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.
Additional administrations of the C-SSRS will be performed at any time during the study if a participant is experiencing psychological distress. If any Since Last Visit C-SSRS reveals an increase in scores past the Baseline assessment (Visit 1 Since Last Visit C-SSRS), the event will be collected as an Adverse Event and seriousness will be evaluated. Sites will be required to notify the Clinical Trial Leader (CTL) and the Medical Monitor as soon as possible.

3.0 Protocol Design

This study protocol will use a randomized, placebo-controlled, double-blind crossover study design to compare the effects of MDMA and placebo in up to 120 participants. Participants can enroll in this study after meeting all inclusion criteria without meeting any exclusion criteria. The investigators will conduct two Experimental Sessions in approved treatment facilities, using the same or similar setting employed in Phase 2 studies of MDMA-assisted psychotherapy for PTSD. Participants will undergo a 1.5-hour Preparatory Session with the investigators the day prior to undergoing the first Experimental Session. Participants will be randomly assigned to one of two conditions and will remain blinded to the condition assignment. Condition 1: Session 1 MDMA, Session 2 Placebo; Condition 2: Session 1 Placebo, Session 2 MDMA. The first Experimental Session will take place at Visit 2. Session dosing will remain blinded throughout the study. The second Experimental Session (Visit 4), will take place at least 48 hours and up to 3 months after the first Experimental Session. During the first Experimental Session depending on condition assignment, participants will receive an initial dose of either placebo or 125 mg MDMA followed by an optional supplemental half-dose of the same compound 1.5 to 2 hours later. For their second Experimental Session, participants will receive MDMA if they received placebo during the first session, and vice versa.

Following each blinded Experimental Session, the participant will stay overnight at the study site or appropriate location approved by site team. Each participant will have a 1.5-hour integrative psychotherapy session on the day after their Experimental Sessions (Visits 3 and 5). The Preparatory Session before the first Experimental Session and the Integrative Sessions after each Experimental Session will serve to prepare the participants for the MDMA experience, while subsequently integrating and addressing any transient distress that may have resulted from the Experimental Sessions. All sessions may be recorded to video so the participant can have a copy for their records, if they request.

Telephone calls for safety follow-up will be made to participants on the day after each Integrative Session (Visit 3 and 5), then every other day for the next 12 days. If the second Experimental Session starts at any time within the 12-day safety follow-up period, no additional safety follow-up is required from the first Experimental Session.

The investigators will then contact the participant by phone at 1 month and 2 months after the second Experimental Session to complete study measures, monitor safety, and help participants understand and integrate their experience.

3.1 Planned Duration of Protocol

The duration of active participation in the protocol will be 2 to 8 months, depending on the duration between Experimental Sessions. The 2-month Follow-up will be considered the termination visit of the protocol. The protocol may remain active up to enrollment of 120 participants.
3.2 Recruitment and Participant Population

The investigators will recruit individuals aged 21 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 in a relevant field, or individuals practicing a related healing profession (physician, nurse, social worker) or other type of relevant practice approved by the MDMA Therapy Training Program. Recruitment will be conducted by invitation only.

3.2.1 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 21 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 prohibited medications (e.g. medications for insomnia or ADHD) prior to Visit 1, and refrain from use until permitted by the research team.
5. Agree that, for approximately 1 week preceding the first 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. Are willing to remain overnight at the study site or appropriate location approved by the site team after each Experimental Session.
9. 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 if they do not remain overnight at the study site.
10. Are willing to be contacted via telephone for all necessary telephone contacts.
11. If of childbearing potential, must have a negative pregnancy test at study entry and prior to each Experimental Session and must agree to use adequate birth control (see Section 7.2.2) from the time of enrollment through 10 days after the last Experimental Session.
12. 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.
13. Must agree to inform the investigator within 48 hours if any medical conditions occur or medical procedures are planned.
15. Agree to not participate in any other interventional clinical trial for the duration of this study.

3.2.2 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 mean of birth control.
3. Any participant presenting current serious suicide risk, as determined through psychiatric 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 [37].
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.

4.0 Methods

Participants will receive consent materials describing the protocol. After consenting to take part in the protocol, participants will be screened by a qualified study team professional (e.g., nurse practitioner, physician). The site physician will obtain medical and psychological history by interview and perform a general physical and brief neurological examination. A site physician will also review electrocardiogram (ECG) and clinical laboratory assessment results (see Section 9.0 Clinical Laboratory Assessments). Further examination will be medical history directed if the investigators have additional questions about participant eligibility. Additional tests or assessments may be requested.

If there is evidence of liver disease by history, physical examination or laboratory testing, hepatitis serology will be performed. If there is evidence of significant hepatic disease other than Hepatitis C the person will not be eligible for enrollment, and will be advised to see their personal physician for further evaluation. 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 relatively stable and of mild severity the person may be enrolled if there are no other contraindications.

If the potential participant has well-controlled hypertension, or a history or current diagnosis of Diabetes Mellitus (Type 1 or Type 2), and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam, or electrocardiogram (ECG), and if the site physician judges their overall health and other cardiovascular risk factors to be acceptable (i.e. family history, smoking, lipid levels, body weight, level of physical activity), they will be referred for exercise testing by a cardiologist and for carotid ultrasound. If these tests fail to reveal evidence of significant vascular disease or other cardiac disease, the person may be enrolled if there are no other contraindications. For participants with either Type 1 or Type 2 diabetes, the site physician may only enroll if after careful evaluation and discussion with the treating physician, if the condition is judged to be stable on effective management, and with approval by the Medical Monitor. Participants with well-controlled hypertension should continue to take their current
antihypertensive medicines as clinically appropriate. The investigators will record and review medications used to control hypertension prior to enrollment.

If, after reviewing all information, the investigators conclude that a participant is eligible, they will schedule study visits. If tapering medication is necessary, the Experimental Session will be scheduled to occur after washout is complete. Eligible participants will travel to the offices of the investigators, where each will have a single 1.5-hour Preparatory Session with the facilitators, followed by the first Experimental Session. Each participant will be assigned to one of two drug administration orders, either receiving MDMA during the first Experimental Session or placebo during this session. A site physician is always on call when a participant is on study. The participant will have a 1.5-hour Integrative Session with the investigators on the morning after each Experimental Session and will be contacted by phone by the facilitators the day after the Integrative Sessions and every other day for the next 12 days for safety follow-up. If the second Experimental Session starts at any time within the first Experimental Session’s safety follow-up period, no additional phone follow-up is required from the first Experimental Session. The second Experimental Session will occur 48 hours and up to 3 months after the first Experimental Session. Participants who received MDMA first will now receive inactive placebo, and vice versa. Participants will be contacted by phone 1 month and 2 months after the second Experimental Session.

4.1 Assessments and Measures

4.1.1 Assessment of Psychological Effects

The POMS-Bi is a 72-item self-report assessment of current mood state [38], containing 6 subscales: Composed-Anxious, Elated-Depressed, Agreeable-Hostile, Energetic-Tired, Clearheaded-Confused, and Confident-Unsure. The POMS-Bi lacks a total score. Participants will complete the POMS-Bi at the beginning of the Preparatory Session, at the end of the Experimental Sessions (6+ hours after drug administration), at the beginning of each Integrative Session, and at the 2-month Follow-up.

The measure of state interpersonal closeness (IPC) is a 5-item non-verbal self-report measure. Participants are asked to draw on a sheet of paper “how close you feel right now” to the self as observed, the investigators, a selected significant other and “the world.” Distance in millimeters between the self and each target will be considered an indirect measure of interpersonal closeness. The measure is expected to take between 2 to 4 minutes to complete. Participants will complete the measures of interpersonal closeness at the beginning of the Preparatory Session and at the end of the two Experimental Sessions (6+ hours after drug administration), and at the beginning of each Integrative Session.

The NEO [39] will serve as a measurement of personality. The NEO is an established 30 to 40-minute, 240-item self-report assessment which may be completed either electronically or by mail. It has sound properties of reliability and validity that operationally define personality structure according to a five-factor model. Participants will complete the NEO at the beginning of the Preparatory Session and again 2 months after the second Experimental Session.

4.1.2 Safety Measures

As safety measures, vital signs and a measurement of psychological distress will be assessed with the Subjective Units of Distress (SUD) scale at the beginning of and during both Experimental Sessions. Participants will rate their current degree of subjective distress during both Experimental Sessions with the degree of distress indicated on a 7-point scale.
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. Blood pressure 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 BSI is the short form of the Symptoms Checklist 90-Revised and is designed to assess clinical and psychological symptoms [40, 41]. It contains 53 items and takes 8 to 12 minutes to complete. It contains 9 dimensions (Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation and Psychoticism) and 3 global indices of distress (Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total). The participants will complete the BSI at the beginning of both the Preparatory Session and the two Experimental Sessions, at the end of the two Experimental Sessions (6+ hours after drug administration), at the beginning of each Integrative Session, and at the 2-month Follow-up.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [42]. 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 once during screening and at the following times after enrollment: at the beginning of both the Preparatory Session and the two Experimental Sessions, at the end of the Experimental Sessions (6+ hours after drug administration), at the beginning of each Integrative Session, the day after each of the Integrative Sessions and then every other day for the next 12 days. If the second Experimental Session starts at any time within the 12-day safety follow-up period, no additional safety follow-up C-SSRS administration are required from the first Experimental Session. The C-SSRS will also be administered at 1 month and 2 months after the second Experimental Session.

The investigators will assess participant wellbeing via interview during all visits or phone contacts through 2 months after the first Experimental Session (Study Termination).

4.1.3 Process Measure

Participant and investigator beliefs concerning substance identity for a preceding Experimental Session (either MDMA or inactive placebo) will be assessed at the beginning of the Integrative Session occurring on the day after each Experimental Session.
### Table 1: Time and Events

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Screening</th>
<th>Preparatory Session</th>
<th>Experimental Sessions</th>
<th>Integrative Session</th>
<th>Post Experimental Session Follow-up</th>
<th>1-month and 2-month Contact</th>
<th>Telephone Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Study</td>
<td>V1</td>
<td>V2 and V4</td>
<td>V3 and V5</td>
<td>Follow-up Contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-month and 2-month Contact</td>
<td></td>
</tr>
<tr>
<td>Visit Timing and Windows</td>
<td>Up to 3 months prior to V1 (may occur over more than 1 day)</td>
<td>1 day prior to V2</td>
<td>Day of dosing (between 48 hours and 3 months apart)</td>
<td>1 day post V2 and V4</td>
<td>1 day post V3 and V5, and every other day for the next 12 days</td>
<td>30 and 60 days post V4 (± 7 days)</td>
<td></td>
</tr>
<tr>
<td>Provide Consent Materials and Informed Consent</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Medical and Psychiatric History (by interview)</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Physical Exam (BP, Pulse, Temp., brief systems check)</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Brief Neurological Exam</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>ECG</td>
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<tr>
<td>Clinical Laboratory Tests (including HIV test)</td>
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<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Collect Concomitant Medication</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Medication Taper (if applicable)</td>
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<td>✓</td>
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</tr>
<tr>
<td>Study Enrollment</td>
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<tr>
<td>Record to Audio/Video (optional)</td>
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<td>✓</td>
<td>✓</td>
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</tr>
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<td>✓</td>
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</tr>
<tr>
<td>Drug and Pregnancy Screen (if applicable)</td>
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<td>✓</td>
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<td>✓</td>
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</tr>
<tr>
<td>Complete Randomization Procedure</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>✓</td>
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</tr>
</tbody>
</table>

A. At end of session (6+ hours post initial drug administration), B. Pre-drug, and/or at the beginning of the session, C. As needed, D. Approximately 2 hours post-drug, before supplemental dose administration, E. If Experimental Sessions are less than 7 days apart, omit from second Experimental Session, F. At the 2-month Contact only, G. Only if related to AEs or SAEs, H. 1 day post V3 and V5 only, I. If the second Experimental Session starts at any time within the first Experimental Session’s safety follow-up period (within the next 12 days following the post V3 phone call), no additional phone follow-up is required from the first Experimental Session, J. If the participant is scheduled for Visit 4 on the day following Visit 3, the investigator should call the participant in the evening of Visit 3 rather than performing this contact on the same day as Visit 4.
4.2 Study Procedures and Visit Descriptions

4.2.1 Screening

Prospective participants may 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 the Screening and Visit Log. 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. The participant will first receive an Informed Consent Form (ICF) by email, mail, or in person, after which an investigator will review the ICF with the participant and answer any questions. 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, as well as a screening number to be recorded in the Screening and Visit Log (if this has not already been done with a pre-screening call).

After consenting to take part in the protocol, participants will be screened by the facilitator and the 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 3 months prior to Visit 1. The entire screening process should take between 1.5 and 2.5 hours. 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 must occur during Screening:

- Medical history, demographics, and psychological history (by interview). The interviewer may require consent to obtain any medical records deemed necessary to clarify or provide more information about medical or psychological history if needed.
- Suicidality assessment by administering C-SSRS.
- Pre-study medications reviewed and recorded.
- A directed physical examination conducted by a qualified study team professional (e.g., nurse practitioner, physician). This examination must include the following:
  - 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 2-12, sensory, motor, reflexes, and cerebellar function)

The participant may provide records from an external care provider prior to their on-site visit for the site physician to review and assess. However, the on-site physical exam will still be required as a screening assessment.

- ECG, which should be evaluated by a qualified physician and results reviewed by the site physician.
- Clinical laboratory assessments (see Section 9.0 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. Laboratory assessments will include:

- Serum electrolytes and metabolic profile
- CBC
- Urinalysis
- Thyroid function
- HIV serology (results should be kept confidential, and appropriate referral for counseling will be made, if necessary)
- Urine-dip pregnancy test for participants of childbearing potential (at sites)
- Urinary drug test will be performed (at sites)

Individuals with well-controlled hypertension, or a history or current diagnosis of Diabetes Mellitus (Type 1 or Type 2), and who are otherwise in good cardiovascular health will be referred for exercise testing and carotid ultrasound to assess for underlying cardiovascular disease.

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 to determine eligibility in the case of positive serology results for Hepatitis C.

There will also be review of any previous substance use to assess abuse, and any pre-study medications will be reviewed and recorded. Lab values may be obtained from outside physicians or laboratories to assess participant eligibility if collected within 12 weeks at the time eligibility is determined. Lab records will be kept with the participant’s Source Records but will not be captured in the electronic Case Report Form (eCRF). Abnormal lab values, however, will be recorded in the medical history portion of the participants Source Record and eCRFs, if clinically significant. Should any part of this examination raise questions about the medical viability of the participant to safely enroll in the study, then an investigator will request a review of the participant’s medical records and any additional tests or assessments that may be indicated. The site physician may also contact outside care providers with participant permission as needed.

A post-screening assessment will be done as quickly as possible, at which point the investigators will review this information and medical records 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 contacted, enrolled in the study, and issued a subject number. The Screening and Visit Log will be updated with the subject number and initials. After the latter process is complete, the investigator will schedule five clinical visits, including the Preparatory Session, the first Experimental Session, the first Integrative Session, the second Experimental Session, and the second Integrative Session. Any participant who takes a specified medication which could interfere with the research must consult with their prescribing physician to begin tapering off that medication, with the first Experimental Session scheduled to occur after complete washout. MDMA will be given on either the first or the second Experimental Session, with investigator and participant remaining blind to order of drug administration.

### 4.2.2 Preparatory Session (Visit 1)

The Preparatory Session may occur on the same day of enrollment, and will occur 1 day before the first Experimental Session. Prior to beginning the Preparatory Session, participants will complete the NEO, POMS-Bi, IPC, BSI, and C-SSRS. The investigator will assess continued eligibility per inclusion/exclusion criteria in Section 3.2.1 and 3.2.2. The investigator will ask necessary questions to ensure that the participant continues to meet eligibility criteria and confirm appropriate medication tapering. After eligibility is confirmed, site staff will request
randomization through the eCRF database to obtain container assignments for the Experimental Sessions.

The participant will then participate in a 1.5-hour Preparatory Session with the investigators, which may be recorded to audio and video if the participant requests for their records. The investigators will begin with an assessment of General Wellbeing, after which the Preparatory Session will consist of the following:

- 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 Sessions, and that specific psychological issues and difficult emotions may arise during Experimental Sessions.
- Remind the participant that difficult emotions, including grief, rage and fear or panic, may arise during Experimental Sessions, 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 each 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 each Experimental Session, and not to use caffeine or nicotine for 2 hours before and 6 hours after drug administration.
- Answer any questions or concerns the participants may have.
- Discuss goals for the Experimental Sessions.

If a participant would like another individual present during one or both of the Experimental Sessions, a meeting between the investigators and that individual will be scheduled during the introductory session. Permission must be granted by the investigators for the presence of another individual during an Experimental Session. All SAEs, AEs leading to withdrawal, and AEs related to changes in psychiatric status will be recorded from the time the participant is enrolled at Visit 1.

4.2.3 Experimental Sessions (Visit 2 and Visit 4)

Experimental Session 1 (Visit 2) will occur 1 day after Visit 1, and Experimental Session 2 (Visit 4) will occur at least 48 hours and not more than 3 months after Experimental Session 1. Each Experimental Session lasts approximately 8 hours (measured from 30 minutes before dosing through 7.5 hours after dosing), followed by an overnight stay at the study site or appropriate location approved by site team. Each participant will receive either MDMA or placebo during the Experimental Sessions as previously described.
Table 2: Schedule of Procedures for Experimental Sessions

<table>
<thead>
<tr>
<th>Approximate Time</th>
<th>Procedure or Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30</td>
<td>Urine Pregnancy Test (if applicable), Participant Acclimated to Environment, BSI, C-SSRS, Urine Drug Screen (Visit 4 drug screen only to be conducted if more than 7 days between Sessions)</td>
</tr>
<tr>
<td>9:45</td>
<td>Baseline Blood Pressure, Temperature, Pulse, SUD</td>
</tr>
<tr>
<td>10:00</td>
<td>Drug Administration, Begin Video Recording (optional)</td>
</tr>
<tr>
<td>12:00</td>
<td>Blood Pressure, Temperature, SUD, Pulse, then Optional Supplemental Dose</td>
</tr>
<tr>
<td>As Needed</td>
<td>Blood Pressure, Temperature, Pulse, SUD</td>
</tr>
<tr>
<td>15:30</td>
<td>C-SSRS, POMS-Bi, IPC, BSI, Blood Pressure, Temperature, Pulse</td>
</tr>
</tbody>
</table>

Prior to IMP administration, the investigator will ensure that container assignment has been obtained from the eCRF database and 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 both Experimental Sessions (if positive, participant will be withdrawn from further Experimental Sessions but may continue non-drug therapy, follow-up, and measures). Urine drug screening will be performed at the beginning of only the first Experimental Session if the second Experimental Session will be conducted less than 7 days later, as MDMA may produce a positive reading for amphetamines, and such a reading on the second Experimental Session could risk unintentional breaking of the blind. If the participant continues to meet criteria and the participant reports that they followed appropriate rules and restrictions, the session will proceed. A positive pregnancy screen is cause for withdrawal from the protocol, while a positive drug screen 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 and BSI approximately 30 minutes before drug administration, and the investigator will record any changes in medication since last visit (including confirmation of medication washout).

In addition, the investigator will confirm that the participant has followed all appropriate rules and restrictions (e.g., no food or 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.

The investigator will assess continued eligibility per inclusion/exclusion criteria in Section 3.2.1 and 3.2.2. If the participant continues to meet criteria and the participant reports that they followed appropriate rules and restrictions, the session will proceed.

The investigators may record both Experimental Sessions to video and audio so the participant may receive any recordings upon request, and the participant will complete the SUD prior to initial dose administration.

At approximately 10:00 AM, participants will receive the initial dose of 125 mg MDMA or equivalent placebo along with a glass of water, and the drug administration will be double-blind. The participant will sit or recline on comfortable furnishings with eyeshades and a program 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 investigators whenever they wish, and will receive guidance and support as needed. If the participant has not spoken within 1 hour, the investigators will inquire briefly about their experience.
Blood pressure, heart rate, body temperature, and SUD will be measured at Baseline prior to drug administration, before the supplemental dose administration, or approximately 2 hours into the session if the supplemental dose is not administered. A supplemental dose of 62.5 mg MDMA, or equivalent placebo, will be administered 1.5 to 2 hours after the initial dose in the absence of contraindications. A final measurement of blood pressure, heart rate, body temperature, and SUD will be taken just prior to ending the session. Blood pressure and pulse 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 Sessions (6+ hours after initial drug administration) the participant will complete the POMS-Bi, IPC, C-SSRS, General Wellbeing, and BSI.

The investigators will also record any spontaneously reported reactions during each Experimental Session, and each effect 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).

A support-individual who has previously agreed and been approved to remain with the participant during an Experimental Session may arrive during the session.

The investigators 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.

The investigators will end video recording (if this was done) when they have established that the participant has returned to Baseline function or is very close to doing so. They complete all Source Records and will record any changes in the participant’s health, such as:

- Spontaneously reported reactions
- All AEs
- SAEs

The participant will remain at the study site (or appropriate location approved by the site team) overnight in a comfortably furnished suite that allows for accompaniment by a significant other, friend, or attendant. A trained attendant will remain with any participants who are unwilling or unable to locate another individual to stay with them at the study site during the overnight stay. Attendants will be selected for their ability to behave reliably and compassionately toward participants while also allowing room for introspection or further self-exploration as needed. All participants will receive instructions for contacting one of the investigators if needed, via telephone or 24-hour pager.

Participants will be instructed not to use caffeine or nicotine for 6 hours after initial drug administration. Participants should also be provided with materials for a narrative report (an optional activity), though they may also use other forms of expression, such as visual art, to represent their experience. The optional narrative report is expected to take between 10 to 30
minutes. Participants may keep their narratives or art. A copy of this report may be kept in the participant file on site, but will not be maintained in the sponsor study files.

4.2.4 Integrative Sessions (Visit 3 and Visit 5)

On each morning after the Experimental Session, the participant will meet with both investigators for a 1.5-hour integrative therapy session to discuss their experience, which may be recorded to audio and video. The participant will complete the POMS-Bi, IPC, BSI, 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 or 5. Both the participant and investigators will indicate their beliefs concerning the identity of the drug the participant received during the Experimental Session (i.e., active vs. placebo).

The discussion during each Integrative Session may include:

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

Whenever possible the investigators will follow the procedures for Integrative Sessions described in the Treatment Manual. If the participant has already generated a narrative report of their experience during an Experimental Session and wishes to share it with the investigators, they may do so at this time. If the participant agrees, the investigators will make a copy of the narrative report to be included in the participant’s site records only, and return the original to the participant. This is expected to take between 10 to 30 minutes. Likewise, participants may use other means of expression, such as visual art, to represent their experience.

The investigators will assess participant mental health via the General Wellbeing measure during the integrative follow-up session and telephone contacts. Investigators will also record changes in medication status and participant health, such as:

- Spontaneously reported reactions
- All AEs
- SAEs

Spontaneously reported reactions will be collected at this visit, and the day following this visit, by phone if necessary. Any reactions continuing outside this period will be recorded and tracked as AEs. If the participant confronted unexpectedly intense or disturbing material during an Experimental Session, the investigators will provide means of continued contact throughout this day as needed.

The participant must have a pre-arranged ride from the study site to the place where they are residing, and if the participant has been unable to arrange transport, then the investigators will assist the participant in locating a ride to the appropriate location.

4.2.5 Phone Contact Following Integrative Sessions

The day after Visit 3 and Visit 5, one or both of the investigators will contact the participant. This telephone contact (or in person visit) will be for a brief check-in lasting 5 to 15 minutes, or as
long as necessary to address any participant’s concerns, administer the C-SSRS, and to assess participant General Wellbeing. The investigator(s) will then record any changes in the participant’s medication status and health, such as:

- Spontaneously reported reactions
- All AEs
- SAEs

If the participant is scheduled for Visit 4 on the day following Visit 3, the investigators should call the participant in the evening of Visit 3 rather than performing this contact on the same day as Visit 4.

After the post Visit 3 and post Visit 5 phone contacts, the investigators will contact the participant by phone for safety follow-up every other day for the next 12 days. If the second Experimental Session starts at any time within this 12-day safety follow-up period, no additional safety follow-up is required from the first Experimental Session. The C-SSRS will be administered during these safety follow-up calls, along with follow-up for any AEs or SAEs as applicable.

Additional contact or an additional Integrative Session can be scheduled at the request of the investigators or participant. Any reactions continuing past this contact will be recorded and tracked as AEs until resolution.

4.2.6 1-Month and 2-Month Integrative Telephone Contact

The investigator will contact the participant 30 and 60 days after the second Experimental Session (Visit 4) plus or minus 7 days. This telephone contact will be for a brief check-in lasting 5 to 15 minutes, but with duration permitted to last as long as necessary to address any participant concerns and to assess the participant’s General Wellbeing, whether undergoing the Experimental Sessions has affected their method of conducting therapy and whether the experience matched their expectations. The investigator will also administer the C-SSRS. The investigator will and record changes in participant health, such as:

- AEs related to changes in psychiatric status
- Clinically significant AEs requiring medical attention
- AEs leading to withdrawal
- SAEs

Medication information will only be recorded if related to AEs or SAEs. Approximately 1 week prior to the 2-month Follow-up, the investigators will mail the participant a copy of the NEO (or it may be completed electronically). The participant will complete the measure and return it in an envelope that uses the offices of the investigators as both mailing and return address. The 2-month phone call will also be considered the termination visit for this protocol. The investigators will collect POMS-Bi and BSI before ensuring that all final safety information is complete, at which point the participant will terminate from the study.

4.3 Randomization and Participant Numbering

Participant numbers will be assigned according to study site. The number assignments will be a unique four-digit code, assigned in ascending order. Participants will be assigned in a blinded fashion to their condition upon enrollment. An unblinded statistician or randomization monitor will generate the randomization list to randomly assign participants with 1:1 allocation to one of
the two sequences of drug administration. Condition assignments will be connected to container numbers in the eCRF database and will be pre-printed on the container labels.

If there is an AE or other emergency requiring knowledge of participant’s condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant. In these cases, the investigator will contact the Randomization Monitor and provide them with the participant number in question, and the Randomization Monitor will inform the investigator of the participant’s condition assignment. In all other cases, the blind will be maintained until all participants have completed the study. The investigators and participant will be blind to condition assignment.

### 4.4 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, it is in the best interest of the participant, if the participant experiences contraindications, or if the participant cannot comply with elements of Experimental Sessions and related visits that are critical for safety. If the investigator withdraws a participant from the session, the investigators 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, Medical Monitor, and/or sponsor. 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 the next Integrative Session(s) and follow-up phone 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.

### 4.5 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. Participants may request recordings of their sessions, if they are still available.

### 5.0 Investigational Medicinal Product

#### 5.1 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 [43, 44]. Phase 2 studies of MDMA-assisted psychotherapy found reductions in PTSD symptoms when compared to inactive placebo or low-dose MDMA [2-5, 7]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased wellbeing, sociability, self-confidence, and extroversion [11, 14-16, 21, 25, 45, 46]. Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with Ecstasy (see for example [15] versus [14]). 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.

5.2 Description of Active Compounds

The active compound to be used in this protocol is MDMA. This ring-substituted phenylisopropylamine has a complex pharmacology but acts most prominently as a monoamine releaser and re-uptake inhibitor [47-49]. Its direct actions on serotonergic, adrenergic, and other receptors are considerably lower. Lactose will serve as the inactive placebo.

5.3 Compounding, Doses, and Labeling

This study employs a randomized, double-blind crossover design. Participants will receive an initial dose of 125 mg of MDMA and an optional supplemental 62.5 mg dose during one of two Experimental Sessions. During the other Experimental Session, they will receive capsules containing an equivalent dose of lactose intended to maintain identical visual appearance and weight. MDMA in bulk will be sent by a Drug Enforcement Administration (DEA)-licensed Schedule 1 Distributor to the Schedule 1 licensed analytical laboratory that will work with the Randomization Monitor for compounding, encapsulation, and labeling.

MDMA will be compounded with lactose as 125 mg and 62.5 mg MDMA doses (calculated as the weight of the hydrochloride salt) to ensure weight and appearance identical to the placebo capsules and placed in gelatin capsules. Lactose, in doses of equivalent dry weight, will be placed into gelatin capsules of identical appearance to those used for MDMA.

Initial and supplemental doses for each Experimental Session will be stored in individual inner envelopes, with each inner envelope holding a single capsule. Two inner envelopes, one initial and one supplemental dose, will be placed within each primary container. Primary containers will be labeled with the protocol number, drug name, lot number, sponsor, and a statement that the drug is for investigational use only. Labels for each dose and each participant will be provided by the sponsor and applied by the analytical laboratory. All packaging and labeling will be done in the presence of a Schedule 1 License Holder.
Example of a container and label that will contain all doses for a participant:

**Figure 1: Examples of Drug Labels**

**Primary Container Outer Labels:**

<table>
<thead>
<tr>
<th>Container Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPS Study: MT1</td>
</tr>
<tr>
<td>Lot #: XXX</td>
</tr>
<tr>
<td>Container #: XXX</td>
</tr>
<tr>
<td>Subject #: ____________</td>
</tr>
<tr>
<td>Experimental Session #: ____________</td>
</tr>
<tr>
<td>Administer as per Protocol - Investigational Use Only</td>
</tr>
</tbody>
</table>

**Primary Container Inner Labels:**

| Stage 1 | Container #: ________ |
| INITIAL DOSE |
| Subject #: ________ | Experimental Session #: ________ |

| Stage 1 | Container #: ________ |
| SUPPLEMENTAL DOSE |
| Subject #: ________ | Experimental Session #: ________ |

**Holding Box Labels:**

<table>
<thead>
<tr>
<th>Holding Box Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPS Study: MT1</td>
</tr>
<tr>
<td>Investigational Product: MDMA</td>
</tr>
<tr>
<td>Dose: 125 mg OR 62.5 mg</td>
</tr>
<tr>
<td>Lot #: XXX</td>
</tr>
<tr>
<td>Administer as per protocol</td>
</tr>
<tr>
<td>Caution: Limited by Law to Investigational Use Only</td>
</tr>
</tbody>
</table>

5.4 **Accountability**

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

5.5 **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 approved designee 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. 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.
5.6 MDMA Stability

Complete details on the chemistry, manufacturing and control of the MDMA hydrochloride (HCl) to be used are described in Drug Master file (DMF) # 6293. As described in that file, MDMA was prepared for human consumption by David Nichols, Ph.D., Department of Medicinal Chemistry and Pharmacology, Purdue University in 1985. The identity and purity of this MDMA was confirmed using High Performance Liquid Chromatography (HPLC) in 1997 as described in DMF # 6293 and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor in relation to the study of MDMA-assisted psychotherapy in people with PTSD, the analysis found it to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart in February, 2006 continued to find a high degree of purity, with the analysis finding the MDMA in question to be 99.9% pure. The latest analyses conducted in May 2017 support that the MDMA is 100.0% pure by HPLC. All required Chemistry Manufacturing and Control (CMC) submissions have been made to the IND.

6.0 Risks in Study Participation

6.1 Non-drug Related Risks

6.1.1 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, 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.

6.1.2 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. 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 also conducted as part of the research 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 current serious suicide risk as determined through psychiatric interview, responses to the C-SSRS (per Inclusion/Exclusion criteria specified in Sections 3.2.1 and 3.2.2), and clinical judgment of the CI.

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 investigators to determine appropriate course of action and will discuss the findings with the participant and their personal therapist, if applicable.
   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 adverse event per Section 7.1 and evaluated for seriousness. SAEs, severe suicidal ideation, self-harm in the context of suicidality, or any suicidal behavior 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, a study team member will call 911. They will explain that the participant is in immediate danger of committing suicide. They will provide a complete description of the participant and give any other needed details to ensure the participant’s safety.
   d. The CI or qualified study team member will notify appropriate members of the study team and sponsor representatives within 24 hours, and provide a narrative for the AE for expedited reporting to the FDA.
   e. The event will be collected as an AE per Section 7.1 and the seriousness will be evaluated. SAEs, severe suicidal ideation, self-harm in the context of suicidality, or any suicidal behavior will be reported per regulatory guidance.

6.1.3 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 provided by the sponsor to record the sessions. If the participant requests, the audio-visual content should be copied to a storage device to be provided to the participant directly after their last on-site psychotherapy study session. If the participant has requested the video while at their last on-site visit, but is not able to stay for retrieval, the site may finish the video transfer to the external storage device and mail the device to the participant’s home address when the transfer is complete. All video content from the participant’s psychotherapy sessions should be deleted from any site storage devices within 2 weeks from the participant’s last on-site visit.

Since the recorded content will not be stored on MAPS equipment, and will be deleted from site storage devices within 2 weeks after the participant’s last on-site visit, 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.

### 6.2 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 Sessions, 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).

#### 6.2.1 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.

#### 6.2.2 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.

#### 6.2.2.1 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 (SBP) but not diastolic blood pressure (DBP). 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 [50, 51].

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 [52]. 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.

6.2.3 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.

6.2.3.1 Psychological Risks and Mitigation

Mild anxiety and depressed mood are occasionally reported 1 to 3 days after MDMA administration [11, 21]. 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 first Experimental Session.
- Creating an atmosphere of trust during the Experimental Sessions.
- Close monitoring.
- Phone contact with participants during the days after the Experimental Sessions.
- 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 Sessions. 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 Sessions, 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.
6.2.3.2 Thermoregulatory Risks and Mitigation

MDMA administered in a controlled setting produces only a slight increase in body temperature \[11\]. 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 \(\degree C\) 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\(^\circ\) 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\(^\circ\) 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\(^\circ\) C above Baseline despite these efforts, the site physician will be consulted for further evaluation and treatment.

6.2.3.3 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 Sessions and fluid intake will be spread out appropriately during the session.

6.2.3.4 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 Sessions.

6.2.3.5 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 \[53, 54\] (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 last Experimental Session and have a negative pregnancy screen before receiving MDMA or placebo in the Experimental Session.

6.2.4 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.
6.2.4.1 Common AEs

Common 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. Prevalence estimates of common AEs in healthy participants collected within this study are listed below, and include both conditions (placebo and MDMA) 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.

6.2.4.2 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [55]. 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 [56]. 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.

6.2.4.3 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, and 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.

7.0 Safety

7.1 Adverse Events

An 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 IMP or not. This definition includes concurrent illnesses/ injuries and exacerbation of pre-existing conditions. An unexpected AE is one that is not listed in the current IB or is by nature more specific or more severe than a listed event.

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 by the investigators until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the CI 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 study 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 the study treatment to an AE will be determined by the CI or study physician using the following definitions:

1. “Not Related”: The AE is not related if exposure to the IMP has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the IMP, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the participant’s pre-existing condition.
2. “Possibly Related”: The administration of the IMP and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the IMP.
3. “Probably Related”: Exposure to the IMP and AE are reasonably related in time and the IMP is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

AEs will be collected as follows for the duration of the protocol:

- SAEs will be collected from enrollment through Study Termination.
- All AEs will be collected on the day of and 2 days after each Experimental Session.
- Clinically significant AEs requiring medical attention will be collected from the first Experimental Session through Study Termination.
- Any AE leading to withdrawal from the protocol will be collected throughout the study.
- AEs related to changes in psychiatric status will be collected throughout the study.
- 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.

7.1.1 Common Expected and Spontaneously Reported Reactions

Commonly expected reactions that are spontaneously reported are collected on a separate eCRF page and will be categorized as mild, moderate or severe. Common, expected reactions are defined as those most frequently reported in the literature and include:

- Anxiety
- Diarrhea
- Difficulty Concentrating
- Dizziness
- Drowsiness
- Dry Mouth
- Fatigue
- Headache
- Heavy Legs
- Impaired Gait/Balance
- Impaired Judgment
- Increased Irritability
- Rumination (increased private worries)
- Insomnia
- Jaw Clenching/Tight Jaw
- Lack of Appetite
- Low Mood
- Muscle Tension
- Nausea
• Need More Sleep
• Nystagmus
• Paresthesia
• Perspiration
• Restlessness
• Sensitivity to Cold
• Thirst
• Weakness

Spontaneously reported reactions will be collected during Experimental Sessions and 2 days after (Day 0-2). This time window was selected based on MDMA’s elimination half-life of 7 to 9 hours, and most reactions are expected to cease within 2 days post-drug in a healthy volunteer population. Any reactions persisting beyond the 2-day window will be recorded and tracked as AEs. Each reported reaction will be actively followed during follow-up phone calls or visits until resolution.

7.1.2 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 Bioavailability/Bioequivalence (BA/BE) Studies, an SAE is defined as any untoward medical occurrence that at any dose:

• Results in death.
• Is life-threatening (i.e. investigator opinion holds that participant is at immediate risk of death from the event as it occurred), but does not refer to an event which might hypothetically 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 which, based upon appropriate medical judgment, may jeopardize the patient/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 an on-study 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 would be due to the onset of the event (the reason for the procedure) having occurred before the participant was entered in the trial. Furthermore, hospitalization for cosmetics, non-emergency prophylaxis, or 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 for the duration of the protocol from enrollment through Study Termination. All SAEs which occur during the course of the trial, whether considered to be
associated with the IMP or not, have to be reported within 24 hours of the site staff’s awareness of occurrence by telephone or email to the study monitor and the Medical Monitors:

    Alia Lilienstein, M.D., M.P.H.
    Medical Director

    Sara Garcia Velazquez, M.D.
    Medical Monitor

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.

7.2 Pregnancy

7.2.1 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.

7.2.2 Pregnancy Contraception Guidelines

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

- Intruterine device (IUD)
- Intruterine 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.

Two forms of contraception are required with any barrier method or oral, vaginal, or transdermal hormones (i.e. condom + diaphragm, condom or diaphragm + spermicide, oral hormonal contraceptives + spermicide or condom). For questions about acceptable birth control methods, contact the Medical Monitor.
7.2.3 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 last Experimental Session. Pregnancies should be reported to the sponsor via telephone or email within 24 hours of site staff awareness.

Participants will undergo a pregnancy test at Screening, and again prior to drug administration during both of the Experimental Sessions. 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 or placebo, and will be discontinued from the study.

In the event of a pregnancy after an 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.

8.0 Concomitant Medications and Tapering Instructions

Participant concomitant medications will be recorded during screening. If necessary, the investigators will make plans for tapering off and discontinuing any prohibited medications at this time, in consultation with the prescribing physician. The investigators will request information about any changes in medication at every visit, except the 1-month and 2-month Follow-up Visits (medication information will only be recorded if related to AEs or SAEs at those times). Medications taken during the course of the protocol, including medications taken to treat AEs, will be recorded on the concomitant medications eCRF.

Participants must be willing to taper off of prohibited medications prior to Enrollment and refrain from use until 40 hours (five half-lives of MDMA) after the second Experimental Session. With a few exceptions, drug washout (5 half-lives) must be completed 1 week prior to the first Experimental Session to allow for a week of psychological stabilization. Tapering will be done in an appropriate fashion to avoid withdrawal effects.

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

- Will refrain from taking any herbal 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 those approved by the research team).

9.0 Clinical Laboratory Assessments

The CI or study physician will examine the laboratory assessments gathered in screening to assess participant eligibility. The investigator or study 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 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)
  - Mean Corpuscular Hemoglobin (MCH)
  - Mean Corpuscular Hemoglobin Concentration (MCHC)
  - Red Cell Distribution Width (RDW)
  - Percentage and absolute differential counts
  - Red blood cell count (RBC)
  - White blood cell count (WBC)

- **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)

- **Urine-dip pregnancy test** for participants of childbearing potential at the study site

- **Urinary drug test** will be performed at the study site
The laboratory assessments, other than the urine drug screen and pregnancy test or any tests performed or ordered previously by the participant’s outside physician, will be performed by LabCorp or an appropriate qualified laboratory.

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 will be performed at the study site.

10.0 Study Monitoring, Auditing, and Documentation

Investigators and/or their study 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 will be performed by the sponsor 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 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.

11.0 Data Analysis

Descriptive statistics will be calculated for all measures. The primary outcome measure of the six POMS-Bi subscale scores will be analyzed by classical methods for crossover studies. The Primary Endpoint analysis will employ a paired t-test at an alpha level of 0.05. A Bonferroni correction will be applied to preserve the overall Type 1 error rate for the 6 hypothesis tests. Exploratory analyses include a repeated measures ANOVA of interpersonal closeness and a paired samples t-test of NEO scores at Baseline and 2-month Follow-up.

Safety analyses include change from Baseline BSI and C-SSRS scores, blood pressure, pulse, and temperature values at specified time points. AEs will be collected according to the Time and Events table and presented as frequency tables. The sponsor will also examine beliefs about condition assignment by computing descriptive statistics and comparisons between those who received MDMA versus placebo during the first session in order to assess strength of blinding for both participants and investigators.

11.1 Statistical Power

The proposed study is a pilot investigation intended to gather data on the effects of MDMA on mood, personality, interpersonal closeness, and psychological symptoms when given in a therapeutic setting. Because of their exploratory nature, pilot studies are often underpowered for detecting the desired effect. Several studies have employed the unipolar version of the POMS, and a review of these studies described effects as robust with an estimated effect size of 0.7 or 0.8
However, the bipolar version of the POMS-Bi was not previously measured in MDMA studies and it lacks a total score.

The sponsor used PASS v14 to calculate 90% estimated statistical power for this crossover study with 120 participants, assuming an effect size of 0.5, and employing a paired t-test at an alpha level of 0.05 with a Bonferroni correction for the 6 hypothesis tests (one for each sub-scale). Statistical power estimates indicate that the study possesses sufficient power to detect differences in mood states with the six POMS-Bi subscales between groups (MDMA vs. placebo). As described in Section 1.2.1 Supporting Information, narrative and anecdotal reports describe greater interpersonal closeness after use of Ecstasy, but the effect is not so readily detected in the laboratory.

12.0 Ethics

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Guidelines for Good Clinical Practice and with applicable local regulations (including US Code of Federal Regulations Title 21).

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.

13.0 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 Experimental Sessions and the participant’s legal rights, the information should hold that access to original medical records and processing of coded personal information must be 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 Sessions and to consider participation.

The ICF must be signed and dated by the participant and countersigned by a qualified study team member providing the ICF review. The investigator will provide a copy of the signed ICF to the participant and maintain the original in the investigator’s study 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 activity is an optional element open only to those completing the MDMA Therapy Training Program for potential therapists conducting MDMA-assisted psychotherapy research, the sponsor may have access to the names of participants as enrollees in the MDMA Therapy 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, ECG testing, 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 medical records, including termination visit information. If a participant revokes only the Health Insurance Portability and Accountability Act (HIPAA) authorization, MAPS will have full access to all of the participant’s medical records prior to the date and time of revocation.

14.0 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of those in the role of research participant, however, despite these efforts, privacy cannot be guaranteed. All data will be identified only by the participant’s initials on the Source Record and four-digit participant number. Copies of audio and video recordings intended for sharing with participants will be marked only with the participant’s identification number. Any materials mailed to participants that require return to the site will be sent along with stamped return envelopes using the office address of the CI both as main and return address. 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 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 (i.e. social security number, etc.). 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.

Each participant may, upon request, receive audio or video recordings of any of the five sessions, including both Experimental Sessions. They may wish to review them as a means of observing and retaining information to support their own reflection on the MDMA-assisted psychotherapy experience. If session recordings are unavailable by the end of their last on-site visit, then the investigators will mail recordings in appropriate packages that list only investigator name and address and otherwise maintain anonymity.

Participants will sign forms for the release of information, such as prior medical records, upon consent to permit screening for protocol enrollment.

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.

Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data (with
or without identifying information). Maintaining data in a secure environment will help prevent
the accidental or deliberate examination or removal of data. While it is possible that individuals
may be identified on audiotape or video recording through means other than their names,
restricting access to audio or video recordings to the participant, and deleting the recordings
within approximately 2 weeks after the last on-site visit, greatly reduces the risk of confidentiality
breach.

15.0 Costs to Participants

Participants will not be charged for any research activities, including any tests or assessments
performed for screening, MDMA used, psychotherapy or intervention administered, or any other
activity or procedure performed in relation to the protocol. If a participant undergoes a medical or
laboratory test solely for the purpose of establishing eligibility for study participation, then the
sponsor will reimburse the full cost of the test or assessment. The sponsor or insurance provider
will be responsible for any payment to treat any study-related injuries, while participants will pay
for any care not related to the protocol. Participants who are not planning on working on MAPS-
sponsored studies will need to pay for travel-related expenses to and from the study location.

16.0 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 in this protocol. If the study
physician cannot treat a study-related emergency, then there are contingency plans for the
transport of participants to the nearest hospital.

17.0 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.
References


