

# MAPS Public Benefit Corporation

## **Protocol and Synopsis MT-1 IND #63,384**

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

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

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STUDY MONITOR	Ben Shechet
USE	In conjunction with relevant FDA guidance

## **MT-1 Protocol Synopsis Amendment 3 Version 1**

### **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**

MT-1

### **Sponsor**

Multidisciplinary Association for Psychedelic Studies (MAPS)  
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### **Investigators**

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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 100 therapists learning to conduct MDMA-assisted psychotherapy. The study will be conducted by male-female co-therapist teams according to the Treatment Manual. The investigators will conduct two Experimental Sessions in treatment facilities at one of two sites, using the same setting employed in their Phase 2 studies of MDMA-assisted psychotherapy for PTSD. 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, followed by an optional supplemental half-dose 1.5 to 2.5 hours later.

Following each Experimental Session, the participant will stay overnight at the study site. 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 on the day after each of the Integrative Sessions, as well as 1 month and 2 months after the second Experimental Session. These will serve as additional opportunities to monitor safety and to help participants understand and integrate the 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 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 2.5 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 therapists training 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, about 6 hours after drug administration on the day of each Experimental Session, at the end of each Integrative Session and at the 2-month Follow-up.

### **Primary Outcome Measure**

POMS-Bi

### **Secondary 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 Measures**

Belief of Condition Assignment and Subject Narrative Account

## **Recruitment and Subject Population**

The investigators will recruit persons aged 21 or older who are learning to conduct MDMA-assisted psychotherapy. Participants will be enrolled at one of two study sites, either in Charleston, South Carolina or Boulder, Colorado. 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 investigators. Participants may have a history of a mood disorder (except bipolar affective disorder type I, see exclusions), anxiety disorder, Attention Deficit Disorders, or other non-excluded psychiatric disorder. Participants with controlled hypertension or asymptomatic Hepatitis C may be enrolled after satisfactory completion of additional screening measures. Participants must be willing to commit to limitations on concomitant medications and to complete study procedures. If the participant is a woman of childbearing potential, she 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 100 participants meeting study criteria will be enrolled. In consultation with their prescribing physician, any individuals taking pre-study medications will taper off these medications, allowing for a washout period of five half-lives of the drug and active metabolites. MDMA will be administered during either the first or the second Experimental Session, with investigator and participant remaining blind to order of condition assignment. Telephone calls will be made to the participant the day after each Integrative Session, as well as follow-up telephone calls 1 month and 2 months after the MDMA session. Preparatory, Experimental, and Integrative Sessions will be video-recorded whenever possible for research purposes.

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-therapist team prior to the first Experimental Session. The co-therapist team 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 one 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 co-therapist team will record any changes in medications. In addition, the co-therapist team will confirm that the participant has followed appropriate rules prior to drug administration. Each Experimental Session lasts approximately 6 to 8 hours and is followed by an overnight stay at the study site. The participant will complete the POMS-Bi, IPC, C-SSRS, and BSI at the end of the Experimental Session, approximately 6 hours after drug administration.

On the morning after each Experimental Session, the participant will meet with the co-therapist team for a 1.5-hour integrative therapy session to discuss his or her 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 co-therapy team 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, and address any important changes. The investigator will also contact the

participant 1 month and 2 months after Experimental Session 2 (Visit 4) and outcome measures will be conducted.

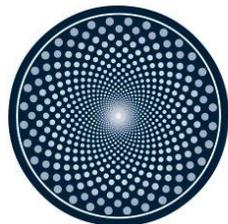
## **Safety**

The safety of participants will be assured during and after the Experimental Sessions by assessing physiological effects, psychological distress, AEs, spontaneously reported reactions, and suicidality:

- Suicidality will be assessed with the C-SSRS prior to Experimental Sessions, twice during Experimental Sessions, and several times after each Experimental Session
- SUD scores and vital signs including blood pressure, heart rate, and body temperature will be measured during each Experimental Session
- BSI will be used to assess clinical and psychological symptoms prior to Experimental Sessions, twice during Experimental Sessions, and after each Experimental Session
- Serious Adverse Events (SAEs) will be collected from enrollment through Study Termination.
- Spontaneously reported reactions will be collected for 2 days after each Experimental Session. Reactions lasting longer than 2 days will be tracked as AEs
- All AEs will be collected on the day of and 1 week 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

## **Statistical Analysis**

Descriptive statistics will be calculated for all measures. The primary outcome measure POMS-Bi scores will be compared by performing a two way repeated measures analysis of variance (ANOVA), with time of administration as repeated measure and condition assignment (placebo, MDMA) as a within-subjects factor. There will be no between-subjects or groups factors. Secondary 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.



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## 1.0 List of Abbreviations

ACLS	Advanced Cardiac Life Support
AE(s)	Adverse Event(s)
ALT/SGPT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
ANOVA	Analysis of Variance
ARCI	Addiction Research Center Inventory
ASC (OAV)	Altered States of Consciousness
AST/SGOT	Aspartate Aminotransferase
BLS	Basic Life Support
BSI	Brief Symptoms Inventory
C	Celsius
CAPS	Clinician Administered PTSD Scale
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HRS	Hallucinogen Rating Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IPC	Interpersonal Closeness Measure
IND	Investigational New Drug
IRB	Institutional Review Board
LSD	d-lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
NEO	Neuroticism-Extroversion-Openness Personality Inventory
NK	Natural Killer
POMS-Bi	Profile of Mood States - Bi Polar Version
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count

RDW	Red Cell Distribution Width
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SERT	Serotonin Transporter
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
VAS	Visual Analog Scale(s)
WBC	White Blood Cell Count

## 2.0 Introduction, Background, and Rationale

### 2.1 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval as a clinical trial sponsor for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. 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). The End-of-Phase 2 meeting with FDA is planned in 2016 to request approval of possible Phase 3 multi-site MDMA/PTSD research studies in 2017. MAPS has published results showing clinically and statistically significant improvements in PTSD severity from 20 participants treated in their first pilot study (MP-1) in the United States (U.S.) [1]. Findings from the long-term follow-up of MP-1 participants suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [2]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) in 12 suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [3]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this population.

This protocol is for a Phase 1 study for up to 100 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, up to 8 hours afterwards [4-6]. 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.

A key limiting factor in the MAPS drug development plan is the need to train significant numbers of male/female co-therapist teams to conduct MDMA/PTSD psychotherapy research in accordance with the Treatment Manual. MAPS is developing group and individual training programs to teach therapists about techniques and procedures for conducting MDMA-assisted psychotherapy for PTSD. The MAPS training programs are designed to support and expand the knowledge and skills of future therapists who will conduct MDMA-assisted psychotherapy.

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 therapists with a training opportunity to experience MDMA in a therapeutic context. The MDMA-assisted psychotherapy used in this Phase 1 study will employ techniques learned in the training program. Receiving MDMA under the direction of investigators will provide participants with an in-depth understanding of how to maximize the therapeutic effects of MDMA. It will also allow participants to better draw distinctions between

common reactions to MDMA-assisted psychotherapy and background events related to medical history.

The MDMA 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 (SOPs). 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.

## **2.2 Background Information**

### **2.2.1 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 investigated alterations of consciousness and mood after MDMA consumption [7, 8], 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 [5, 6, 9, 10]. 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 [4, 5]. 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. 11, 12-14].

Some researchers have specifically assessed the acute effects of MDMA with the Profile of Mood States measure [6, 7, 10]. Of these studies, only one has assessed mood the morning after nocturnally administered MDMA [6]. A few investigators have examined sub-acute effects, but generally as self-reported reactions and not effects on mood [5, 15]. 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 therapists 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 therapists. Listening to music is often part of the experience, as is the option to use eyeshades during the session. Participants remain at the study site overnight and work with the therapists 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 [16, 17], 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 [12, 13, 18]. 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 [15, 19, 20], 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 [21], 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 degree 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 [6, 7, 10], 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 both shortly before drug administration and as drug effects are waning, as well as during the days before and after the session.

Enrollment in this study will be limited to a maximum of 100 therapists learning to conduct MDMA-assisted psychotherapy. 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 [22]. 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 [23].

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 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 [24-26]. 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 IND for d-lysergic acid diethylamide [27] 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 his ability as a therapist from undergoing a supervised experience with LSD [28].

### **2.2.2 Previous MDMA Research**

As of December 2015, MDMA has been administered to approximately 1185 research participants, in both Phase 1 and Phase 2 studies, without any occurrences of unexpected drug-related Serious Adverse Events (SAEs) [4, 6, 29-39].

The initial and supplemental doses of MDMA to be used in this protocol are identical to those in use in the studies of MDMA-assisted psychotherapy research completed or currently underway in the U.S., Switzerland, Canada, and Israel. Previous researchers have also used doses within this range [5, 9, 15, 29, 36].

Only three human trials of MDMA have attempted to assess empathy or interpersonal closeness, an affect 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.

### **2.3 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

protocol will now include two sites, one in Charleston, South Carolina, and the other in Boulder, Colorado.

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, MAPS is conducting a training program intended to teach therapists how to conduct MDMA-assisted psychotherapy in preparation for the Phase 3 program and other research studies, 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 therapists who are engaged in learning to conduct MDMA-assisted psychotherapy 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.

### **3.0 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 therapists training to conduct MDMA-assisted psychotherapy research.

#### **3.1 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, about 6 hours after drug administration on the day of each Experimental Session, at the end of each Integrative Session, and at the 2-month Follow-up

#### **3.2 Secondary Objectives**

The protocol will meet the following secondary and 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 MDMA administration using the NEO Personality Inventory

#### **3.3 Safety Objectives**

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, and AEs.

- 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, on the first day of telephone contact, and 1 month and 2 months after the first Experimental Session
- SUD and vital signs (blood pressure, heart rate and temperature) will be measured during each Experimental Session. Comparisons will be made for vital signs by condition.
- Spontaneously reported reactions 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 two-day window will be recorded and tracked as AEs.
- To assess psychological symptoms and monitor for safety, participants will complete the BSI will be used to assess clinical and psychological symptoms on the day of the Preparatory Session, twice on the day of each Experimental Session (before drug administration and 5 to 6 hours afterwards), on the day of each Integrative Session, and at the 2-month Follow-up
- SAEs will be collected from enrollment through Study Termination
- All AEs will be collected on the day of and 1 week after each Experimental Session.
- Clinically significant AEs requiring medical attention will be collected from the first Experimental Session through Study Termination
- Any Adverse Event (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

Additional administrations of the C-SSRS will be performed at other points following drug administration or during follow-up telephone contact if a participant is experiencing psychological distress that does not respond readily to processing with the therapists according to the methods described in the Treatment Manual.

#### **4.0 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 100 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 treatment facilities at one of two sites, using the same 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 Experimental Sessions 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 2.5 hours later. Following each blinded Experimental Session, the participant will stay overnight at the study site. Each participant will have a 1.5-hour integrative psychotherapy session on the day after their Experimental Sessions (Visits 3 and 5). On the day after the first Integrative Session (Visit 3) (or on a subsequent day within 3 months of Visit 2) participants will undergo a second Experimental Session (Visit 4), receiving MDMA if they received placebo during the first session and *vice versa*. 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 will be recorded to video whenever possible, and participants may view videos of their sessions upon request. Telephone calls will be made to participants on the day after each Integrative Session (Visit 3 and 5), as well as 1 month and 2 months after the second Experimental Session. These will serve as additional opportunities to monitor safety and to help participants understand and integrate the experience.

#### **4.1 Planned Duration of Protocol**

The duration of active participation in the protocol will be 2 to 5 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 100 participants.

#### **4.2 Recruitment and Participant Population**

The investigators will recruit men and women 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. 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 investigators.

##### **4.2.1 Inclusion Criteria**

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

1. Are learning to conduct MDMA-assisted psychotherapy
2. Are at least 21 years old
3. Must be generally healthy
4. Must sign a medical release for the investigators to communicate directly with their therapist and doctors
5. Are willing to refrain from taking psychiatric medications during the study period
6. Are willing to follow restrictions and guidelines concerning consumption of food, beverages, and nicotine the night before and just prior to each Experimental Session
7. Are willing to remain overnight at the study site after each Experimental Session
8. Agree to have transportation other than driving themselves home or to where they are staying after the Integrative Session on the day after each Experimental Session
9. Are willing to be contacted via telephone for all necessary telephone contacts
10. Must have a negative pregnancy test if able to bear children and agree to use effective birth control
11. Must provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by the investigator in the event of an emergency

12. Must agree to inform the investigator within 48 hours of any medical conditions and procedures
13. Are proficient in speaking and reading English
14. Agree to have all clinic visit sessions recorded to audio and video
15. Agree to not participate in any other interventional clinical trials for the duration of this study

#### **4.2.2 Exclusion Criteria**

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

1. Are pregnant or nursing, or if able to bear children and are not practicing an effective means of birth control
2. Weigh less than 48 kg
3. Are abusing illegal drugs
4. Are not able to give adequate informed consent
5. Upon review of past and current drugs/medications, are on or have taken a medication that is exclusionary
6. Upon review of medical or psychiatric history, any current or past diagnosis that would be considered a risk to participation in the study

#### **5.0 Methods**

Participants will receive consent materials describing the protocol.

After consenting to take part in the protocol, participants will be screened by a physician who will obtain medical and psychological history by interview and perform a general physical examination, brief neurological exam, and clinical laboratory assessments (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, he or she 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 and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam, or electrocardiogram (ECG), and if the CI 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. Participants taking one or more antihypertensive may be enrolled in the study. The investigators will record and review medications used to control hypertension prior to enrollment. Any enrolled participants with hypertension will be treated by a therapy team comprised of at least one licensed physician.

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 investigators, 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. 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 therapists the day after the Integrative Sessions. 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.

## **5.1 Assessments and Measures**

### **5.1.1 Assessment of Psychological Effects**

The POMS-Bi is a 65-item self-report assessment of current mood state [41], containing 6 subscales Composed-Anxious, Elated-Depressed, Agreeable-Hostile, Energetic-Tired, Clearheaded-Confused, and Confident-Unsure. Participants will complete the POMS-Bi at the beginning of both the Preparatory Session and the two Experimental Sessions, 5 to 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 5 to 6 hours after drug administration at the two Experimental Sessions, and at each Integrative Session.

The NEO [42] 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 after completing the Preparatory Session and again 2 months after the second Experimental Session.

### **5.1.2 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 seven-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 [43, 44]. 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, 5 to 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 [45]. 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 ten times after enrollment: at the beginning of both the Preparatory Session and the two Experimental Sessions, 5 to 6 hours after drug administration, at the beginning of each Integrative Session, on the first day of telephone contact, as well as 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).

### **5.1.3 Process Measures**

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. On the second Integrative Session, participants and investigators will also be asked if they changed their minds about their original guesses concerning drug administered during the first Experimental Session.

On the evening of Visit 2 and Visit 4, for both research and educational purposes, the investigators will require participants to produce a written narrative account of each Experimental Session. This is expected to take between 10 to 30 minutes. Participants may also use other means of expression, such as visual art, to represent their experience.

**Table 1: Time and Events**

Visit Number	Pre-Study	V1	V2 and V4 <sup>F</sup>	V3 and V5	Follow-up Contact	1-month and 2-month Contact
Type of Visit	Screening	Preparatory Session	Experimental Sessions	Integrative Session	Post Experimental Session Follow-up	Telephone Follow-up
Visit Timing and Windows	Up to 1 month prior to V1 (may occur over more than 1 day)	1 day prior to V2	Day of dosing (between 48 hours and 3 months apart)	1 day post V2 and V4	1 day post V3 and V5	30 and 60 days post V4 (± 3 days)
Provide Consent Materials and Informed Consent	✓					
Medical and Psychiatric History (by interview)	✓					
General Physical Exam (BP, Pulse, Temp., brief systems check)	✓					
Brief Neurological Exam	✓					
ECG	✓					
Clinical Laboratory Tests (including HIV test)	✓					
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓
Medication Taper (if applicable)	✓	✓				
Study Enrollment		✓				
Record to Audio/Video		✓	✓	✓		
General Wellbeing		✓	✓	✓	✓	✓
Drug Screen	✓		✓ <sup>E</sup>			
Pregnancy Screen (if applicable)	✓		✓			
Complete Randomization Procedure		✓				
NEO Personality Inventory		✓				2-month Contact Only
POMS-Bi		✓	✓ <sup>A</sup>	✓ <sup>B</sup>		2-month Contact Only
BSI		✓	✓ <sup>A, B</sup>	✓ <sup>B</sup>		2-month Contact Only
IPC		✓	✓ <sup>A</sup>	✓ <sup>B</sup>		
C-SSRS	✓	✓	✓ <sup>A, B, C</sup>	✓ <sup>B</sup>	✓	✓
Administer Drug and Therapy			✓			
Monitoring of BP, Pulse, and Temp.			✓ <sup>A, B, C, D</sup>			
SUDS			✓ <sup>A, B, C, D</sup>			
Belief of Condition Assignment				✓		
Overnight Stay			✓			
Integrative Therapy Session				✓		
Narrative Report (optional)			✓			
Telephone Contact					✓	✓
Adverse Events Requiring Medical Attention			✓	✓	✓	
Spontaneously Reported Reactions			✓	✓	✓	
Adverse Events that Concern the Participant			✓	✓	✓	✓
Serious Adverse Events		✓	✓	✓	✓	✓
Study Termination						✓

<sup>A</sup> Approximately 6 hours post-drug, <sup>B</sup> Pre-drug, at the beginning of the session, <sup>C</sup> As needed, <sup>D</sup> Approximately 2 hours post-drug, before supplemental dose administration, <sup>E</sup> If Experimental Sessions are less than 7 days apart, omit from second Experimental Session

## 5.2 Study Procedures and Visit Descriptions

### 5.2.1 Screening

Screening can occur over more than 1 day and up to 1 month prior to Visit 1. The entire screening process should take between 1.5 and 2.5 hours. All of the following must occur during Screening:

- 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 Log.
- Procure participant medical history (by interview)
- Procure participant psychological history (by interview)
- Assess suicidality by administering C-SSRS

A directed physical examination will be conducted by a physician who is not a member of the treating therapist team. This examination may supplement a prior physical examination conducted by external care providers and should include:

- Blood pressure and pulse
- Height, weight, and body temperature
- Examination of head, eyes, ears, nose, and throat
- Examination of skin, heart, lungs, abdomen, and extremities
- Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes, and cerebellar function)
- ECG

Individuals with well-controlled hypertension, and who are otherwise in good cardiovascular health will be referred for exercise testing and carotid ultrasound to assess for underlying cardiovascular disease. Participants who are determined to be eligible and who have well-controlled hypertension will be treated in the study by a therapy team comprised of at least one licensed physician.

Clinical laboratory assessments (See Section 9.0 Clinical Laboratory Assessments):

- 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 females of childbearing potential (at sites)
- Urinary drug test will be performed (at sites)

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.

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 upon their arrival. The Screening Log and Subject Log will both be updated with the subject number and initials, which will also be added to the Visit Tracking Log. 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.

### **5.2.2 Preparatory Session (Visit 1)**

The Preparatory Session 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 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. 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.
- Participants will be reminded 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 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.

### 5.2.3 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 (followed by an overnight stay at the study site). Each participant will receive either MDMA or placebo during the Experimental Sessions as previously described.

**Table 2: Schedule of Procedures for Experimental Sessions**

Approximate Time	Procedure or Action
9:00	Urine Pregnancy Test, Participant Acclimated to Environment, BSI, C-SSRS, Urine Drug Screen if Less than 7 Days between Sessions
9:45	Baseline Blood Pressure, Temperature, Pulse, SUD
10:00	Drug Administration, Begin Video Recording
12:00	Blood Pressure, Temperature, SUD, Pulse, Optional Supplemental Dose
As Needed	Blood Pressure, Temperature, Pulse, SUD
16:00	C-SSRS, POMS-Bi, IPC, BSI, Blood Pressure, Temperature, Pulse

Prior to IP administration, the investigator will ensure that container assignment has been obtained from the eCRF database and the participant will arrive approximately 1-hour before the start of each Experimental Session.

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). 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 he/she 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 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 (i.e. no food or beverage after midnight, etc.), 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 investigators will record both Experimental Sessions to video and audio (the participant may view 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, at the time of 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 2.5 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 the participant experiences significant psychological distress which does not respond to processing with the therapists, the C-SSRS may be administered. Approximately 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 recording 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 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 drug administration. Participants should also be provided with materials for a narrative report, though they may also use other forms of expression, such as visual art, to represent their experience.

### **5.2.4 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 his or her experience, which will be recorded. The participant will complete the POMS-Bi, IPC, BSI, and C-SSRS just prior to beginning the Integrative Session, at which point 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 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. The investigators will make a copy of the narrative report to be included in the Source Records 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 she or he is 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.

### **5.2.5 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 and to assess participant wellbeing. The investigator(s) will then record any changes in the participant's medication status and health, such as:

- General Wellbeing
- Spontaneously reported reactions
- All AEs
- SAEs

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. The C-SSRS will be collected via phone at this contact as well.

### **5.2.6 1-Month and 2-Month Integrative Telephone Contact**

The investigator will contact the participant 30 and 60 days after the second Experimental Session (Visit 2) plus or minus 3 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 his or her method of conducting therapy, and whether the experience matched his or her expectations. The investigator will also administer the C-SSRS and record both changes in medication status and participant health, such as:

- General Wellbeing
- AEs related to changes in psychiatric status
- Clinically significant AEs requiring medical attention
- AEs leading to withdrawal
- 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.

## **5.3 Randomization and Participant Numbering**

Participant numbers will be assigned according to study site, with participants at the Charleston, SC site receiving numbering as "1101, 1102," etc. and participants at the Boulder, CO site receiving numbering as "2101, 2102," etc. 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.

#### **5.4 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 his or her 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 him or her 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.

#### **5.5 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 still view recordings of sessions if they request them.

### **6.0 Investigational Product**

#### **6.1 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 [46, 47]. In the first completed study of MDMA-assisted psychotherapy in people with PTSD, the principal investigator reported reduction in PTSD symptoms, as assessed by an independent rater, in people who received MDMA with psychotherapy instead of placebo [1]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased wellbeing, sociability, self-confidence, and extroversion [5, 8-10, 15, 19, 48, 49]. Findings in samples of largely drug-naïve individuals are similar to those

reported by people with previous experience with ecstasy (see for example [9] versus [8]). 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.

## **6.2 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 [50-52]. Its direct actions on serotonergic, adrenergic, and other receptors are considerably lower. Lactose will serve as the inactive placebo.

## **6.3 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 DEA-licensed Schedule 1 Distributor to the Schedule 1 License Holder who will work with the Randomization Monitor and the pharmacist for compounding, encapsulation, and labeling. The Schedule 1 License Holder will oversee the process in a manner that will maintain the study blind.

The pharmacist will provide bulk lactose for compounding. 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 pharmacist. All packaging and labeling will be done in the presence of the 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:

Container Label
MAPS Study: MT-1
Lot #: XXX
Container #: XXX
Subject #: _____
Experimental Session #: _____
Administer as per Protocol - Investigational Use Only

Primary Container Inner Labels:

Stage 1	Container #: _____
<b>INITIAL DOSE</b>	
Subject #: _____	Experimental Session #: _____

Stage 1	Container #: _____
<b>SUPPLEMENTAL DOSE</b>	
Subject #: _____	Experimental Session #: _____

Holding Box Labels:

Holding Box Label
MAPS Study: MT-1
Investigational Product: MDMA
Dose: 125 mg OR 62.5 mg
Lot #: XXX
Administer as per protocol
Caution: Limited by Law to Investigational Use Only

## 6.4 Accountability

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

## 6.5 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 safe which has been inspected and approved by the DEA for this purpose. Only the Schedule 1 License Holder will have access to the safe. The room in which the safe is placed will have an alarm system and be locked whenever the Schedule 1 License Holder or a study investigator is not present.

Investigational product will only be removed from the safe once per participant at the time of the session, and the MDMA will not leave the premises. 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.

## **6.6 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.

## **7.0 Risks in Study Participation**

### **7.1 Risks and Discomforts Associated with Screening**

Medical data will be collected via medical and psychiatric history interview, general physical examination, and additional tests, assessments or interviews, if applicable. Submitting to a full medical examination and psychiatric assessment may be time-consuming, distressing, or uncomfortable for some. These procedures are intended to ensure that only those without any contraindicated conditions for receiving MDMA are enrolled. Because medical history, physical examination, and the collection of laboratory specimens are all part of the screening procedure, they cannot be omitted from the protocol design.

### **7.2 Risks and Discomforts Associated with Psychotherapy Sessions and Assessment of Measures**

In preparation for drug-assisted psychotherapy sessions, blood draws and a physical examination are required to establish eligibility for the study. Temporary discomfort, inflammation, or infection could arise due to of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

During screening, non-drug and drug-assisted psychotherapy sessions, and administration of study measures, some measures contain items that may provoke negative emotions. It is possible that completing these measures could be upsetting. Psychotherapy is also conducted as part of the research study, including the experimental intervention, and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and, memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

All psychotherapy sessions may be recorded to audio and video for research and training purposes. Participants may feel uncomfortable with having their sessions recorded. Participants may request to view their recordings. These recordings will be stored at the sites in locked storage to ensure confidentiality. Researchers, IRBs, and regulatory agencies may view these recordings, and participants will have control over any presentation of this material beyond these parties.

### **7.2.1 Safety Plan and Procedures for Participants Who Screen Positive for Suicidal Ideation or Intent**

The CI will minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with a history of suicide attempts will not be excluded unless risk of suicidal behavior is present at the time of the screening assessment. Participants will be enrolled according to the Inclusion/Exclusion criteria based on the clinical judgment of the CI. After enrollment, data on General Wellbeing will be collected at each visit on the participant's current demeanor and state of mind and risk of deterioration. The CI or qualified designee will administer the C-SSRS according to the Time and Events table, and as needed depending on clinical presentation of the participants, to monitor for development and intensity of suicidal ideation and/or behavior. The therapist 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 4 or greater), indicating risk at the time of the assessment, or positive Suicidal Behavior (Scores of 1 or greater) then 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 therapist 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 phone or in person will be continued until the participant has stabilized or a new course of action is taken based on changes in C-SSRS score and/or ongoing clinical assessment.
  - c. If this finding is treatment-emergent and clinically significant, the event will be collected as an AE.
  - d. Treatment would be continued when deemed appropriate by the CI and Medical Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up.
2. If the participant has suicidal ideation, and a plan to commit suicide (Suicidal Ideation Score=5) or positive Suicidal Behavior (Score greater than or equal to 1), the therapist administering the C-SSRS will assess whether the risk is imminent. A Suicidal Ideation score of 5 does not necessarily indicate an immediate risk if the thoughts are fleeting, fairly easily controlled, and deterrents are strong. If there is no imminent risk, the therapist will follow the procedure described in number 1. If there is imminent risk of suicidal behavior, the therapist will ensure:
  - a. Participants are evaluated to determine appropriate course of action, and the study therapist will contact their personal therapist or come to the study site for a visit, depending on their location
  - 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
    - ii. Escort the participant to an appropriate mental health services facility (e.g. hospital psychiatric unit) or
    - iii. Call 911 and ensure that the participant is transferred to the responding medical personnel
  - c. If the participant will not comply and wishes to leave without consultation, call 911. Explain that the participant is in immediate danger of committing suicide. Provide a complete description of the participant and give any other needed details to ensure the participant's safety.
  - d. Notify appropriate members of the study team and Sponsor representatives

- e. If this finding is treatment-emergent and clinically significant, the event will be collected as an AE and the seriousness will be evaluated. SAEs will be reported per FDA guidance.
- f. Treatment would be continued when deemed appropriate by the CI and Medical Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up

### **7.2.2 Risks of Receiving MDMA**

Spontaneously reported reactions and common adverse effects of MDMA are modest and have generally not been associated with serious discomfort by healthy volunteers in previous studies. Common reactions include lack of appetite, insomnia, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, ruminations, and thirst. Other slightly less common reactions include restlessness, parasthesias (odd somatic feelings, such as tingling, feeling hot or cold), impaired judgment, perspiration, drowsiness, and nystagmus (eye-wiggling). While anxiety, headache, fatigue, insomnia and lack of appetite were spontaneously reported by 40% to 80% of participants in both conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by participants in the MDMA than the placebo condition, and irritability was slightly more likely to be reported in the placebo condition. Additionally, participants in the MDMA condition were more likely to report muscle tension in various body parts and diarrhea.

These effects are transient and diminish as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, needing more sleep, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects are reported less often than acute effects. More information on spontaneously reported reactions is described in the IB.

MDMA may produce mild alterations in sensory perception and altered perception of time [4, 8, 9]. Women may be more sensitive to these effects [5]. MDMA acutely affects attention, information processing, and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of complex scene changes [34]. For this reason, participants will stay at the site overnight and will not be permitted to drive after Experimental Sessions.

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness.

For further information on the risks associated with MDMA, including information drawn from case reports and studies of users, see the IB.

### **7.2.3 Cardiovascular and Sympathomimetic Effects**

The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 1.5 to 2.5 hours, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. These changes should last no more than 6 hours. In less than 5% of volunteers in Phase 1 studies, peak blood pressure values were higher than 140/90 mmHg. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of participants and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity. For more information, see the IB.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing uncontrolled hypertension and monitoring blood pressure and pulse, as described in Section 5.1.2 Safety Measures. Individuals with controlled hypertension will be required to undergo additional screening procedures to rule out occult cardiovascular disease. During Experimental Sessions, the co-therapists will continually evaluate the patient for signs or symptoms of a developing hypertensive or other cardiovascular emergency. Participants reporting chest pain, shortness of breath, neurological symptoms, or other potential indicators of hypertensive emergency or any other serious medical problem will have more frequent measurements and assessment by the study physician. Any participant who experiences medical complications during an Experimental Session will not be given another Experimental Session unless it is approved by the CI, study physician, and the Medical Monitor.

In case of need, participants will be transferred to the emergency department at the closest hospital, as described in Section 8.5 Medical Emergencies. Reasons for moving a patient to an Emergency Department (ED) would include, but not be limited to, severe headache in the setting of hypertension, angina, or neurological deficits regardless of blood pressure. The CIs and study physician may, at any time, make a clinical judgment to transfer the patient to the ED for closer monitoring and additional treatment.

The study physician will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). The therapists will attend to any signs or symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress, and will notify the study physician if this occurs for on-site evaluation or a decision to initiate transfer to the ED. If any participant has neurological deficits, as assessed by the study physician, whether or not they are associated with hypertensive crisis, they will receive oxygen, and vital signs and general condition will be closely monitored pending transfer to the hospital. If necessary, they will be transported to the emergency department at the closest hospital for further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [53].

The therapists will observe the participants and note any complaints of chest pain. If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, they will receive heart rhythm monitoring, oxygen and will be monitored as described above. If necessary, they will be transported to the ED or a location in the hospital where appropriate care can be given. 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 patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [54].

#### **7.2.4 Psychological Distress**

Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following an MDMA 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 modest and self-limiting, while responding well to reassurance from investigators with occasional use of benzodiazepines for

anxiety. In the proposed protocol, participants may confront emotionally intense or upsetting memories, thoughts, and feelings. Signs of psychological distress, panic, or other unpleasant psychological reactions may not be as strong as expected in people with psychiatric disorders, but may still be present. The investigators will be monitoring degree of psychological distress during the MDMA session with the SUDS and via observation. The investigators will be collecting Baseline, 2 hours after administration, and endpoint SUDS for each participant on the eCRFs. Less commonly, mild anxiety and depressed mood are reported 1 to 3 days after MDMA administration [5, 15](see the IB). Some of these effects are likely to occur, but it is expected that proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute reactions.

### **7.2.5 Body Temperature**

MDMA administered in a controlled setting produces only a slight increase in body temperature [5], and ambient temperature does not enhance or attenuate this slight elevation in humans [29]. If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and directing a fan toward the participant, if necessary.

### **7.2.6 Reproductive and Developmental Risks**

Risks posed by MDMA to pregnant women 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 [55, 56] (see the IB).

Pregnant and lactating women will be excluded from participation in the study, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session while also agreeing to use adequate birth control for the treatment portion of the study.

### **7.2.7 Potential Neurotoxicity Associated with Ecstasy Use**

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials. The current scientific literature has taken careful steps to minimize effects of methodological limitations of previous research and found only modest evidence of neurotoxicity. The sponsor has considered the risks and conclude the risk of neurotoxicity is minimal in this study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with lack of toxicity reported in previous MDMA clinical studies. More information on the potential for neurotoxicity of MDMA is described in the IB.

### **7.2.8 Risk Mitigation**

Careful review of medical screening data will be utilized to exclude potential participants with pre-existing exclusionary medical conditions from the study. Study procedures have been developed to mitigate the risks of receiving MDMA, as described in the IB. Ambient temperatures will be kept at a comfortable level during Experimental Sessions. Participants will not be allowed to drink more than 3 L of fluids over the course of the Experimental Session, and fluid intake will be spread out appropriately during the session. Fluids administered will include electrolytes. If a participant exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions, they will not be given another Experimental Session unless it is approved by the CI, study physician, and the Medical Monitor.

### **7.3 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. More information on abuse liability is described in the IB.

Whether MDMA-assisted psychotherapy will cause some PTSD patients to develop an MDMA use disorder is an open question that the sponsor is addressing on an ongoing basis. Based on long-term follow-up data from two sponsor-supported studies (N=32), only one participant took Ecstasy after completing the study and failed to reproduce the experience from the study, and a number of participants volunteered that they would never seek out Ecstasy outside a legal, controlled, therapeutic setting. In addition, negative results from MDMA-specific drug testing data obtained from the Swiss study MP-2 (N=12) supports that none of these participants took Ecstasy outside of the study during the long-term follow-up period.

Diversion is not an issue in this protocol because MDMA will only be administered a few times under the supervision of the CI and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

## **8.0 Adverse Events**

### **8.1 Adverse Events**

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant resulting from the administration of a pharmaceutical product at any dose, and 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 product, whether considered to be related to the investigational product 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. 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 investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no

- facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition
2. "Possibly Related": The administration of the investigational product and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product
  3. "Probably Related": Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE

AEs that will be collected for the duration of the protocol are:

- SAEs will be collected from enrollment through Study Termination
- All AEs will be collected on the day of and 1 week 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

## **8.2 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
- Parasthesias
- 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.

### **8.3 Serious Adverse Events**

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), 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.

### **8.4 Adverse Event Collection**

All SAEs will be collected for the duration of the protocol beginning with the first visit. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours (or on the following working day at the latest) by telephone or fax to either of the following:

Medical Monitor:

Julie Holland, MD

Study Monitor:

Ben Shechet

## **8.5 Medical Emergencies**

The Preparatory, Experimental, and Integrative Sessions will all be conducted in the psychiatric offices of the investigators. In South Carolina, the offices are located 2.6 miles from the nearest emergency department. In Boulder, the offices are located 1.2 miles from the nearest emergency department. The study physician will be available at both sites in case of medical emergencies, and will either be on-site or a maximum of three miles from the site during Experimental Sessions.

With these personnel and equipment, the therapists or study physician will be able to perform basic cardiac life support if necessary and call Emergency Medical Services (EMS) to transport the participant to the ED at the closest hospital. In the event of a medical emergency or any other medical problem, the study physician will be immediately available in person or by phone, and based on his assessment of the situation, he will make the decision to either evaluate the participant himself at the site, have the therapists call EMS to transport the participant to the ED, or instruct the therapists to take the participant to the ED where he will meet them.

For a recently completed Phase 2 trial, the researchers established (in communication with the FDA) contingency plans for responding to the AEs that appear most likely to occur based on a comprehensive review of case reports of toxicity in illicit MDMA users found by Baggott and colleagues in 2001 and in the current IB. The same contingency plans and equipment will be used in this protocol, and with these personnel and equipment, the researchers would be able to stabilize a participant in the office and then transport him or her by ambulance if hospital admission were required.

## **9.0 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 contraindicated medication at this time, in consultation with the prescribing physician. The investigators will request information about any changes in medication just prior to the first Experimental Session. 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 refrain from taking any psychiatric medications from study enrollment until 7 days after the second Experimental Session, with the exception of gabapentin prescribed for pain control. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects and will be discontinued long enough before the first Experimental Session (i.e. five times the half-life of the drug in question) to avoid the possibility of interactions. Participants may be administered a designated rescue medication in response to symptoms experienced during or after an Experimental Session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the Treatment Manual). Participants must agree that, for 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)

## **10.0 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
  - ALT/SGPT
  - Albumin:globulin (A:G) ratio
  - Albumin, serum
  - Alkaline phosphatase, serum
  - 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
  - MCV
  - MCH
  - MCHC
  - RDW
  - Percentage and absolute differential counts
  - RBC
  - Red blood cell count
  - White blood cell count
- Urinalysis
  - Color
  - Appearance
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Occult blood
  - Leukocyte esterase
  - Nitrite
  - Bilirubin
  - Urobilinogen
- Thyroid function
  - TSH high sensitivity
  - Free T4
  - Free T3
- HIV serology
- Urine-dip pregnancy test for females of childbearing potential
- 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.

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.

## **11.0 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 each monitoring visit, source data verification will be performed by a Clinical Research Associate (CRA) 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.

## **12.0 Data Analysis**

Descriptive statistics will be calculated for all measures. The primary outcome measure POMS-Bi scores will be compared by performing a two way repeated measures analysis of variance (ANOVA), with time of administration as repeated measure and condition assignment (placebo, MDMA) as a within-subjects factor. There will be no between-subjects or groups factors. Secondary 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.

### **12.1 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 POMS-Bi, and a review of these studies described effects as robust [4]. These findings suggest an estimated effect size of 0.7 to 0.8.

The sponsor used Java applications created by Lenth to calculate estimated statistical power for this study, assuming an effect size of 0.7 and employing a paired t-test as a means of examining estimated power in a crossover study with 100 participants [57]. Statistical power estimates indicate that the study possesses sufficient power to detect differences in mood between MDMA and placebo within-subjects. As described in Section 2.2.1 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.

### **13.0 Ethics**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The protocol and the ICF must be reviewed and approved by a properly constituted 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 his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor.

### **14.0 Informed Consent**

The CI is 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 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 the CI. 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 session. The communication of this information should be documented. Because this activity is an optional element open only to those completing a sponsor-developed training program for potential therapists conducting MDMA-assisted psychotherapy research, the sponsor may have access to the names of participants as enrollees in the training program. However, only the participant numbers and participant identification codes will be recorded in the eCRF. Written consent to take part in the MDMA session includes giving the investigators permission to view the participant's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

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

## **15.0 Confidentiality**

Every effort will be made to strictly safeguard the confidentiality of those in the role of research participant, though 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 subject number. Any materials mailed to participants will be sent along with stamped return envelopes using the office address of the CI both as main and return address. 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.).

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 performance of MDMA-assisted psychotherapy research. If session recordings are unavailable by the end of the Integrative Session, 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.

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 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 researchers greatly reduces the risk of confidentiality breach.

## **16.0 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.

## **17.0 Treatment and Compensation for Study Related Injury**

Treatment of a study-related emergency would first be billed to a participant's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a participant's health insurance. Some study-related emergencies can be treated by the investigators, as described under Section 8.5 Medical Emergencies. If the study physician cannot treat a study-related emergency, then there are contingency plans for the transport of participants to the nearest hospital.

## **18.0 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.

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