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1.0 List of Abbreviations

ACLS	Advanced Cardiac Life Support
AE(s)	Adverse Event(s)
AED	Automated external defibrillator
AMI	Acute Myocardial Infarction
BDI-II	Beck Depression Inventory II
BLS	Basic Life Support
BP	Blood pressure
BT	Body temperature
C	Celsius
CAPS	Clinician Administered PTSD Scale
CI	Clinical Investigator (e.g. therapists, co-investigators)
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Agency
ECG/EKG	Electrocardiogram
EMS	Emergency Medical Services
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IV	intra-venous
LSD	d-lysergic acid diethylamide
MAOI	Monoamine oxidase inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MDMA	3,4-methylenedioxymethamphetamine
MP-1	MAPS' first clinical trial of MDMA-assisted psychotherapy for PTSD
PDS	Posttraumatic Diagnostic Scale
PTSD	Posttraumatic Stress Disorder
PRN	As needed
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RRPQ	Reactions to Research Participation Questionnaire
SAE(s)	Serious Adverse Event(s)
SCID	Structured Clinical Interview for Diagnoses

SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
U.S.	United States of America

2.0 Introduction, Background and Rationale

2.1 Introduction

This protocol is a Multidisciplinary Association for Psychedelic Studies (MAPS)-sponsored proof-of-principle Phase 2 clinical study. It will investigate the effects of an additional 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy session in up to three participants with PTSD who relapsed after their PTSD symptoms had significantly decreased during MAPS' initial U.S. Phase 2 trial testing the use of MDMA-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder (PTSD). This new protocol will consist of a single, full-dose open-label session of MDMA-assisted psychotherapy, along with associated non-drug preparation and integrative psychotherapy sessions.

MAPS is a U.S.-based IRS-approved non-profit research and educational organization that sponsors research into the therapeutic potential of MDMA, other psychedelic compounds, and marijuana. MAPS' top priority project is working to obtain approval for the prescription use of MDMA-assisted psychotherapy in patients with posttraumatic stress disorder (PTSD). MAPS is currently sponsoring a Phase 2 study in the U.S. in veterans with chronic, treatment-resistant, war-related PTSD.

MAPS' initial U.S. MDMA/PTSD study has been completed, with promising results published in the *Journal of Psychopharmacology* [2]. Findings from the long-term follow-up portion of the study, evaluating subjects at an average of 41 months post-treatment, suggest that the therapeutic benefits were sustained as measured by the Clinician Administered PTSD Scale (CAPS). Upon completion of the treatment portion of the study, average CAPS scores two months after two sessions of MDMA-assisted psychotherapy were 28.47 +/- 21.33 (n = 19). This is slightly higher than the average CAPS scores of 23.69 +/- 22.77 (n = 16) at the long-term follow-up, with scores at both timepoints under the cut-off of 50 points for study inclusion. While most of the subjects' symptoms continued to improve or stayed roughly the same from the two-month follow-up to the long-term follow-up, two subjects had relapsed. These results are being prepared for submission to FDA and publication in a peer-reviewed journal.

MAPS U.S. studies are part of an international series of Phase 2 studies designed to evaluate safety and efficacy of MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD for possible use as an approved prescription medication in the U.S., Europe and Israel [1]. MAPS' Swiss pilot study was completed in early 2011, with the data currently being prepared for publication. MDMA was administered without evidence of harm and generated promising data about efficacy. Additional pilot studies are in the approval process in Canada, Jordan and Israel.

2.2 Background

2.2.1 Posttraumatic Stress Disorder (PTSD)

PTSD is a debilitating psychiatric disorder arising after a traumatic life event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. The DSM-IV[3] criteria for PTSD include:

- A. Exposure to a significant traumatic event accompanied by an intense acute emotional response.
- B. Persistent re-experiencing of the event or aspects of the experience.
- C. Persistent avoidance of stimuli associated with the event, and/or withdrawal from some aspects of life.
- D. Persistent symptoms of increased arousal.
- E. The above symptoms must last for more than one month for Acute PTSD and more than three months for Chronic PTSD.

PTSD is a worldwide public health problem for which a wider array of effective treatments is needed. The lifetime prevalence of PTSD in the U.S. general population is between 6 and 10% [4-8], but it is common in other countries as well [5, 9-12]. According to some estimates, PTSD appears to be less prevalent in the general population of Europe at 1.9% [13]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [14], and it is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [15]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [16-18].

The search for novel and more effective treatments is of major public health and economic significance. PTSD is typically a chronic illness [6, 19] associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [5-8]. People with PTSD face challenges in relationships and work productivity [20]. In the U.S. National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In both subgroups, more than a third of the patients still had symptoms several times per week after 10 years [4]. Forty to 60% of PTSD patients were found to be resistant to treatment in this study. In a comparison of two types of psychotherapy for women with PTSD after sexual assault in 2002, 47% of each treatment group was still diagnosed with PTSD after treatment, based on high Clinician Administered PTSD Scale (CAPS) scores [21].

Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [22]. PTSD treatment goals include alleviating symptoms and correcting stress-induced neurochemical abnormalities associated with the condition. Two selective serotonin reuptake inhibitors (SSRI), sertraline and paroxetine, are currently marketed as PTSD medications in the U.S. These drugs are known to affect the serotonergic components of PTSD, but it is not known whether they can arrest and reverse the hippocampal atrophy found in individuals with PTSD [34]. In addition, SSRIs affect PTSD symptoms in a dosage dependent manner and they must be used every day in order to be effective [23].

Another treatment approach is to develop drugs and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD [28], although some patients may need more than one treatment to reduce or resolve those symptoms [20]. A recent meta-analysis concluded that all “bona fide” psychotherapies, including those listed above, are similarly effective with PTSD [29].

At least a third of PTSD patients fail to respond to established PTSD psychotherapies or respond in a way that falls outside of clinical significance [24-26]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [27], and another randomized, double-blind study found no difference between sertraline and placebo in the treatment of PTSD [28]. These findings suggest that there is still a substantial need for innovative treatments for PTSD. In recent years, there has been a growing amount of research into drugs and other methods that may augment the effectiveness of psychotherapy for PTSD (see [29] for a review). Examples of this are virtual reality-assisted exposure therapy [30, 31] and D-cycloserine-assisted psychotherapy [32]. MDMA-assisted psychotherapy is another example of such emergent treatments.

2.2.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the psychedelic drug mescaline. It was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s [33, 34]. In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was placed in Schedule 1 in 1985 as a result of extensive non-medical use [35-37]. Placement in Schedule 1 prohibited it for use except in a federally approved research setting.

Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [38-42]. Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can “reduce or somehow eliminate fear of a perceived threat to one’s emotional integrity” [39]. Elimination of these “conditioned fear responses” can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some clinicians and researchers have asserted that MDMA may increase empathy or compassion for self and others, decrease defensiveness and help to strengthen a therapeutic alliance with psychotherapists, and that the above factors taken together can

provide the opportunity for a corrective emotional experience [39]. Some investigators suggest that MDMA should be categorized as part of a new class of psychotropic agents referred to as entactogens [43]. The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others.

2.2.3 Previous Clinical Experience with MDMA

Classification as a Schedule 1 drug hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and efficacy of MDMA-assisted psychotherapy has become more feasible [1, 44, 45]. The first double-blind, placebo controlled U.S. Phase 1 study sanctioned by the FDA was conducted in 1994, with findings that suggested that MDMA caused a significant increase in body temperature and heart rate in some healthy volunteers [46]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting [46]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well-tolerated by healthy individuals [47].

The potentially therapeutic effects of MDMA were initially investigated starting in 2000 in a MAPS-sponsored dose-response pilot study in Spain in women survivors of sexual assault with treatment-resistant PTSD [48, 49]. Unfortunately, the study in Spain was halted in 2002 due to political pressure from the Madrid Anti-Drug Authority. Prior to its suspension, six women were enrolled and treated in this study without any adverse events or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 to 75 mg [49].

As of 2011, MDMA has been administered to approximately 510 research participants, in both Phase 1 and Phase 2 studies, without any occurrences of drug-related Serious Adverse Events (SAEs) [50-68]. In the context of psychotherapy, MDMA has been noted to reduce defensiveness and fear of emotional injury while enhancing communication and capacity for introspection [35].

MAPS recently completed its first U.S. study of MDMA-assisted psychotherapy for the treatment of PTSD, known as MP-1. This study employed the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded independent rater at baseline, 3 to 5 days after each experimental (MDMA or placebo) session, and two months after the final experimental session. All participants in this study tolerated MDMA well, and MP-1 data suggests that MDMA is associated with significantly greater improvement in PTSD than placebo [2]. Findings from the long-term follow-up evaluating the US subjects at an average of 41 months post-treatment, suggests that the therapeutic benefits have been sustained over time [69]. The sponsor has also supported a randomized, double-blind study of MDMA-assisted psychotherapy in twelve subjects with PTSD in Switzerland.

2.2.4 MDMA-assisted Psychotherapy for PTSD

MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that may enhance or amplify certain aspects of psychotherapy. MDMA possesses unique pharmacological properties that may make it especially well suited for use as an adjunct to psychotherapy in PTSD patients [37, 39-41]. In contrast to daily administrations of SSRIs, this treatment consists of several sessions of MDMA-assisted psychotherapy within the context of a moderate course of non-drug psychotherapy.

Treatment goals of MDMA-assisted psychotherapy for PTSD include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. Reports of past experience with MDMA-assisted psychotherapy suggest that it may also counteract the effects of PTSD. In fact, the biologic and psychotherapeutic approaches overlap and reinforce each other. Knowledge about the connections between the neurobiological and the therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala [70]. This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [71, 72]. MDMA also elevates oxytocin and changes brain activity in response to fearful and happy faces [51, 73].

A comprehensive review of MDMA research is included in the Investigator's Brochure supplied by the Sponsor. This document should be reviewed prior to initiating the protocol.

2.3 Protocol Purpose

This proof-of-principal Phase 2 open-label study will investigate the effects of a single session of MDMA-assisted psychotherapy in up to three subjects who relapsed after their PTSD symptom severity had significantly decreased following treatment with MDMA-assisted psychotherapy in the course of the MAPS sponsored MP-1 study. Up to three subjects, who either had a global CAPS severity score of ≥ 50 at a long-term follow-up (1 year or more) after completing MP-1, or who spontaneously contacted the clinical investigator to report the worsening symptoms and were subsequently found to have a CAPS score of ≥ 50 , will be enrolled in the study. All participants will receive a full dose of MDMA (125 mg possibly followed by 62.5 mg of MDMA) used as an adjunct to manualized psychotherapy. Participants will have one preparatory session prior to the MDMA-assisted session and three integrative sessions afterwards. The extent of PTSD symptoms, as well as depression symptoms and general psychological well-being, will be assessed at baseline, and at 2 month and 12 month follow-ups by a clinician and through the use of self-report measures. The study will investigate whether a single additional session of MDMA-assisted therapy can ameliorate relapse of PTSD in the study subjects.

2.4 Rationale of Dose Selection

The study subjects will be administered the full dose of MDMA, consisting of 125 mg given initially, possibly followed one and a half to two and a half hours later by 62.5 mg, unless contraindicated based on safety measures.

Table 1. Dose Regimen

	Initial Dose	Supplemental Dose	Cumulative Dose
Full MDMA Dose	125 mg	62.5 mg	187.5 mg

The full MDMA dose to be used in this study is identical to those used in previous MAPS-sponsored studies in the U.S., Switzerland and Israel. Previous researchers had also used doses within this range [46, 47, 53, 60, 74-79]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [35, 37, 41]. The initial full dose is expected to produce all the commonly reported effects of MDMA. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. All subjects in this study will have previously tolerated a dose of at least 125 mg during their participation in the original Phase 2 trial.

3.0 Protocol Objectives

The objective of this study is to investigate whether a single session of MDMA-assisted psychotherapy can ameliorate the relapse of PTSD in those subjects who had improved during participation in a Phase 2 clinical trial evaluating the safety and efficacy of MDMA-assisted psychotherapy but whose PTSD symptoms worsened over time during the follow-up period or after the initial study.

3.1 Primary Objective

- Assess changes in PTSD symptoms in relapsed subjects receiving a single session of MDMA-assisted psychotherapy as measured via CAPS score at baseline and at 2 months and 12 months after the session.

3.2 Secondary Objectives

- Assess changes in self-reported PTSD symptoms in relapsed subjects receiving a single session of MDMA-assisted psychotherapy as measured via Posttraumatic Diagnostic Scale (PDS) score at baseline, at 2 months and 12 months after the experimental session.
- Assess depression symptoms via the Beck Depression Inventory-II (BDI-II) at baseline and at 2 months and 12 months after the experimental session.
- Assess quality of life via the Global Assessment of Functioning (GAF) at baseline and at 2 months and 12 months after the experimental session.

- Explore self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Assess the participant's experience as a research subject, perceived reasons for consenting to be a research participant and perceived freedom to take part in the study via the Reactions to Research Participation Questionnaire (RRPQ).
- Assess long-term benefits and harms of study participation by completing the long-term follow-up questionnaire.

3.3 Safety Objectives

The safety objectives of the study are to monitor and assure safety of subjects during and after the experimental session by assessing physiological effects, psychological distress, adverse events, spontaneously reported reactions and suicidality.

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) at screening, twice during the experimental session, and several times after the experimental session.
- Vital signs including blood pressure, heart rate and temperature, and the degree of psychological distress will be assessed periodically during the experimental session.
- Serious adverse events, adverse events and spontaneously reported reactions will be collected during the study according to Section 8.5.

4.0 Protocol Design

This open-label proof-of-principle study will examine the effects of a single session of MDMA-assisted psychotherapy in up to three subjects with current PTSD who relapsed after the initial improvement they had experienced during the Phase 2 clinical trial testing MDMA in conjunction with psychotherapy. The study will include one MDMA-assisted psychotherapy session, referred to as an experimental session, with a male/female co-therapist team. Subjects will meet with their therapist team for one preparatory session, conducted prior to the experimental session. Participants will complete the SOCQ after the experimental session. The experimental session will be followed by an overnight stay at the clinic, an integrative psychotherapy session the next day and two additional integrative sessions.

Symptoms will be assessed by an independent rater as well as using self-report measures. The independent rater will assess PTSD symptoms with the CAPS, quality of life with the GAF, and subjects will complete the BDI-II to measure symptoms of depression. The subjects will complete the PDS, a self-report measure of their PTSD symptoms, to assess symptoms via a self-report measure developed to assess the same diagnostic criteria as the primary outcome measure. Baseline assessments will be compared with the assessments made at the follow-ups. (See Table 2 Time and Events).

At each visit with the investigators, suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS), in addition to general well being. Adverse Events and Concomitant Medications will be collected as described in Section 8.5 and 9.0 of the protocol.

4.1 Planned Duration of Study

The duration of the study for each subject will be approximately 12.5 months after enrollment.

Summary of Events

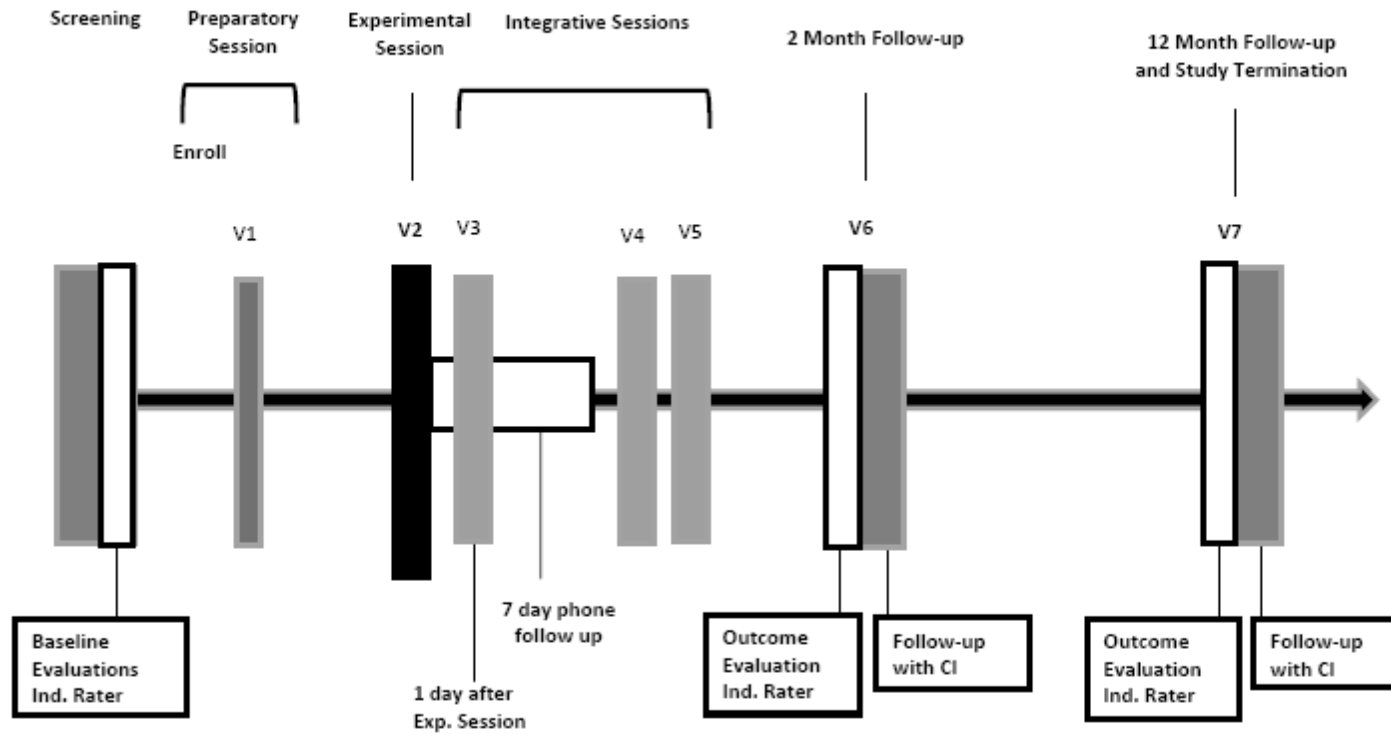


Table 2. Time & Events	Screen/Baseline	Preparatory	Experimental Session	Integrative Session 1	Integrative Session 2	Integrative Session 3	2 Month Follow-Up	12 Month Follow-Up
Visit #	Prior to Enrollment	V1	V2	V3	V4	V5	V6	V7
Type of Visit	Baseline Screening may take place over more than one day up to one month prior to Visit 2	Preparatory Session	Experimental Session	Integrative Session	Integrative Session	Integrative Session	Follow-up & Outcome	Follow-up & Outcome
Visit Timing or Study day or Window		May be completed during screening	After V1	Next day after V2	After V3 before V5	After V4 before V6	2 months after V2	12 months after V2
Informed Consent	X							
View Medical Records	X							
Consult physician or therapist	X							
Collect Concomitant Medications	X	X	X	X	X	X	X	X
Medication Taper (if applicable)			X ^A					
Drug Screen	X		X					
Pregnancy Screen (if applicable)	X		X					
CAPS, GAF, BDI-II, PDS (with Ind. Rater)	X						X	X
Study Enrollment after meeting I/E			X ^A					
Record to Audio/Video		X	X	X	X	X		
General Well-Being		X	X ^B	X ^F	X	X	X	X
C-SSRS	X	X	X ^{B, C, D}	X ^I	X	X	X	X
Administer IP Drug + Therapy			X					
Monitoring of BP, Pulse and Temp.			X					
SUD			X ^{C, E}					
SOCQ			X ^H					
Overnight Stay			X ^H					
Integrative Therapy Session				X	X	X		
7 days Integrative Telephone Contact				X ^F				
AEs Requiring Medical Attention			X	X	X	X	X	
Spontaneously Reported Reactions and all AEs			X ^G	X ^{F, G}	X ^G	X ^G		
AEs related to changes in psychiatric status or withdrawal		X	X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X	X
RRPQ							X	
Long-term follow-up questionnaire								X
Termination								X

A = Prior to V2 after medical records are received B = Approximately 6 hours post MDMA C = At the beginning of the session D = As needed E = Approximately every 60-90 minutes F = For 7 days post Exp. Session, G = Spontaneously reported reactions will be collected on the day of MDMA administration and for seven days after the Exp. Session H = After the Exp. Session I = During V3 and Day 2 and Day 7 of calls post Experimental Session

4.2 Recruitment and Subject Population

Participants may be up to three men or women who completed MAPS Phase 2 clinical trial MP-1, the initial pilot study of MDMA-assisted psychotherapy, and who in the course of long-term evaluation or spontaneously indicated to the clinical investigator the relapse of PTSD symptoms. Participants should have a confirmed diagnosis of current PTSD at screening with a CAPS score equal to or greater than 50, and must meet all the inclusion criteria and none of the exclusion criteria. Participants must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA.

4.2.1 Inclusion Criteria

Summarized Criteria for Posting

Inclusion Criteria:

1. Be diagnosed with chronic PTSD;
2. Have a CAPS score showing moderate to severe PTSD symptoms;
3. Have participated in MP-1;
4. Are at least 18 years old;
5. Must be generally healthy;
6. Must sign a medical release for the investigators to communicate directly with their therapist and doctors;
7. Are willing to refrain from taking any psychiatric medications during the study period;
8. Willing to follow restrictions and guidelines concerning consumption of food, beverages, and nicotine the night before and just prior to each experimental session;
9. Willing to remain overnight at the study site;
10. Agree to have transportation other than driving themselves home or to where they are staying after the integrative session on the day after the MDMA session;
11. are willing to be contacted via telephone for all necessary telephone contacts;
12. Must have a negative pregnancy test if able to bear children, and agree to use an effective form of birth control;
13. must provide a contact in the event of a participant becoming suicidal;
14. Are proficient in speaking and reading English;
15. agree to have all clinic visit sessions recorded to audio and video
16. Agree not to participate in any other interventional clinical trials during 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 a woman who can have children, those who are not practicing an effective means of birth control;
2. Weigh less than 48 kg;

3. Are abusing illegal drugs;
4. Are unable to give adequate informed consent;
5. Upon review of past and current drugs/medication must not be on or have taken a medication that is exclusionary.
6. Upon review of medical or psychiatric history must not have any current or past diagnosis that would be considered a risk to participation in the study.

5.0 Methods

5.1 Measures

The following outcome and safety measures will be used in this research study:

5.1.1 Outcome Measures

The primary outcome measure will be the CAPS, a clinician-scored measure for PTSD diagnosis and symptom intensity and severity. A qualified, blinded independent rater will perform the CAPS. The independent rater will not be present during the subject's experimental session and will not have any information regarding the experimental session. The CAPS provides a standardized method to evaluate the frequency and intensity dimensions of each symptom, impact of symptoms on the subject's social and occupational functioning, overall severity of the symptom complex and global improvement since baseline, and the validity of the ratings obtained. The CAPS interview takes approximately one hour to complete. The CAPS has been determined to have good internal consistency, concurrent validity, and test/retest reliability [80, 81]. An independent rater will assess all subjects according to the Time and Events table.

The secondary measure of PTSD symptoms will be the PDS, a self-report measure designed to follow DSM IV criteria for assessing PTSD. The measure is derived from the Posttraumatic Symptom Scale – Self Report (PSS-SR), a measure also intended to tap into diagnostic criteria for PTSD. The PDS contains 49 items, with responses made on a four-point scale, ranging from 0 (“not at all”) to 3 (“five or more times a week”). The PDS consists of a list of 12 potential traumatic events, 12 items addressing elements of the traumatic event, 17 symptom items, and 9 items assessing impact on areas of life function [82]. Items addressing elements of the traumatic event and life function are answered as either present or not present (Yes or No). The seventeen symptom items are summed to create a symptom severity scale. Cronbach's alpha for the symptom severity scale is 0.92. The PDS has test-retest reliability of 0.74 after a two-week and one-month interval, and subscales are inter-correlated, with correlations ranging from 0.73 to 0.82, and PDS scores have a moderate to good correlation with SCID diagnosis, with kappa = 0.65 [82]. Subjects will complete the PDS at the same times as the CAPS.

The Beck Depression Inventory-II (BDI-II) is a 1996 revision of the BDI, a 21-item self-report measure [83, 84], that will serve as a measure of depression according to DSM-IV criteria [85]. The BDI-II has been validated, has high internal consistency and good

test/re-test reliability and is not overly sensitive to daily variations in mood. It takes five to ten minutes to complete [85]. Subjects will complete the BDI-II at the same times as the CAPS.

The Global Assessment of Functioning (GAF) is a measure of quality of life and general function made through observations. The GAF consists of a single score on the scale from 0 to 100, with 100 reflecting superior function and zero reflecting serious risk of causing harm to the self or others. The GAF is a reliable, validated measure of social functioning [86]. Subjects will complete the GAF at the same time as the CAPS.

The States of Consciousness Questionnaire (SOCQ) is a 100-item questionnaire based on the “Peak Experience Profile” designed by Pahnke and colleagues [87, 88]. Participants respond to the SOCQ using a five-point Likert-type scale anchored at 0=none at all and 5=extreme (“more than ever before in my life”). It has seven subscale scores: internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. The measure is a self-report instrument and takes approximately 20 to 30 minutes to complete. Participants will complete the SOCQ as a process measure once after the experimental session in the interval between the end of an experimental session and prior to leaving the treatment facility the next day.

The Reactions to Research Participation Questionnaire (RRPQ) [89] is an assessment of causes for taking part in research and responses to the experience of being a research subject. Subjects will complete this measure during their final study visit. The RRPQ is a process measure intended to assess the subject’s experience as a research subject, perceived reasons for consenting to be a research subject and perceived freedom to take part in the study, and is not an outcome measure.

A long-term follow-up questionnaire that has been developed internally by the Sponsor to assess long-term benefits and harms of MDMA-assisted psychotherapy will be completed by the study subjects at the 12 month follow-up visit. It contains questions on benefits and harms from taking part in the study, questions concerning psychotherapy and medications within the period between the two month and 12 month follow up, and substance use during this time period. It takes between five and ten minutes to complete.

All psychotherapy sessions, including the experimental session, will be recorded to audio and video, with all recordings preserved for research and training purposes.

5.1.2 Safety Measures

Safety measures, vital signs and a measurement of psychological distress will be assessed during the experimental session.

Subjects will rate their current degree of subjective distress with the SUD scale, a single-item, self-report scale, repeatedly during the experimental session, with the degree of distress marked along a seven point Likert scale.

The C-SSRS is a measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during the clinical trial [90]. 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 a face-to-face interview or over the telephone. The investigators will assess suicidality at baseline, twice during the experimental session, once during each integrative session, during the second and seventh day of the telephone contact, and once during the 2-month and 12-month follow-ups.. The C-SSRS data will be reported on Case Report Forms (CRFs) for all administrations except for the second integrative session, unless an increase in suicidality is observed by the investigators. C-SSRS data from the second integrative session will be kept with the subject’s source record.

The investigators will assess general wellbeing during the preparatory session, on each integrative session and integrative telephone calls for seven days, and at 2-month and 12-month follow-ups.

Blood pressure and heart rate will be assessed periodically during the experimental session. Blood pressure and pulse will be measured at the outset of the experimental session, and once approximately every 30 minutes during the experimental session. More frequent measures will be taken if the investigators judge them to be medically indicated. Participants with controlled hypertension will have blood pressure and pulse assessed every 15 minutes for the first five hours and every 30 minutes for the next three hours. Blood pressure will also be measured more frequently if there are clinical symptoms, such as chest pain, shortness of breath or neurological symptoms that may be indicative of hypertension. The investigators will measure the subject’s body temperature approximately every 60 to 90 minutes. The timing of these measurements will be adjusted so that they do not interfere with the therapeutic process.

All AEs and spontaneously reported reactions will be collected as described in section 8.5. Adverse events and spontaneously reported reactions may be collected during face to face visits or over the telephone. Common spontaneously reported reactions will be collected for seven days after the experimental session on a separate CRF page and will be categorized as mild, moderate or severe.

5.2 Study Procedures and Visit Descriptions

5.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study)

All individuals who enter screening, as defined in this section, should be assigned a screening number and recorded on the “subject screening log” where information on the selection of potential subjects in the trial should be collected. The subject screening number should also be recorded on the subject’s informed consent form. If a subject is enrolled, the study staff should record the enrollment date and assign a subject number. If a subject is not enrolled, an explanation should be recorded on the screening log. A CRF will not be completed for subjects who are not enrolled. These subjects will only be documented on the screening log and source records. It is the responsibility of the investigator to file the screening log in the investigator site file (ISF) to be readily available for on-site monitoring and/or inspection by relevant authorities. Screening may take place over more than one day and up to one month prior to Visit 2. If, after reviewing all information, the investigator concludes that the subject is eligible, the subject will be enrolled in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

- a. Explain and obtain written informed consent from the subject. Written informed consent must be obtained prior to performing any tests or evaluations for the study.
- b. Assign the subject a screening number. Complete the screening log.
- c. Conduct a clinical interview about any changes the subject may have had in medical or psychiatric history since participation in MP-1 study.
- d. Request the review of the subject’s records to screen for any conditions listed in the eligibility criteria of this research protocol and contact the subject’s treating physicians to obtain additional information as needed.
- e. 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 subject 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.
- f. If the potential subject has well-controlled hypertension and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam or ECG, and if the investigator judges their overall health and other cardiovascular risk factors to be acceptable (family history, smoking, lipid levels, body weight, level of physical activity), they will be referred for exercise testing by a cardiologist and for carotid ultrasound. If these tests fail to reveal evidence of significant vascular disease or other cardiac disease, the person may be enrolled if there are no other contraindications. Participants taking one or more antihypertensives may be enrolled

in the study. The investigators will record and review medications used to control hypertension prior to enrollment.

- g. Review the ability of females of childbearing potential to become pregnant and their commitment to practice appropriate birth control as determined by the investigator for the total duration of the study.
- h. Administer the following tests:
 - Urine-dip pregnancy test on females with childbearing potential
 - Urine drug screen
 - C-SSRS to assess suicide risk

An independent rater who will not be present during any of the therapy sessions will administer:

- CAPS to assess PTSD symptoms and determine eligibility
- PDS to assess self-reported PTSD symptoms
- BDI-II to assess depression symptoms
- GAF to assess general psychological function

5.2.2 Preparatory Psychotherapy Session (Visit 1)

The preparatory session may take place before enrollment.

- a. Record preparatory sessions to audio and video. Subjects may receive copies of audio or video recordings from the preparatory session upon request.
- b. AEs and medications will be recorded as described in Sections 8.5 and 9.0 of the protocol.
- c. Assess the subject's general wellbeing.
- d. Administer the C-SSRS.
- e. The subject will undergo a preparatory session, lasting 60-90 minutes, with a male and female co-therapist team. The investigators will work with the subject to prepare him or her for the experimental session. The investigators will seek to form a strong therapeutic alliance with the subject and will help the subject prepare for the upcoming experimental session. The preparatory session will promote a safe setting for confronting trauma-related memories, emotions and thoughts.
- f. The subject and the investigators will discuss goals for the experimental session and will review what will happen during the experimental session, following standard procedures and techniques discussed in the Sponsor's treatment manual.
- g. During the preparatory session the investigators will introduce the subject to the attendant that will remain with the subject during the overnight stay after the MDMA-assisted psychotherapy session. The attendant will be an individual with previous training in managing psychological distress.
- h. If a subject would like another individual present during or after the experimental session, a meeting between the investigators and that individual will be scheduled prior to the experimental session. There must be mutual agreement between the subject and the investigators concerning the presence of the support individual.
- i. The investigators will give the Subject Information Sheet to the subject, which includes instructions and restrictions for conduct 24 hours prior to receiving the

MDMA, including restrictions on food and alcohol consumption. Subjects must agree to take:

- Nothing by mouth except alcohol-free liquids after 24:00 (midnight) the evening before the experimental session.
- Subjects must also refrain from the use of any psychoactive drugs, with the exception of caffeine or nicotine, within 24 hours of each experimental session.
- Subjects must not use caffeine or nicotine for 2 hours before and 6 hours after ingesting the drug, or until investigators deem it safe to do so.

5.2.3 Experimental Session (Visit 2)

Subjects who do not complete all screening activities will not be enrolled. If all inclusion criteria and no exclusion criteria are met, eligibility will be confirmed with the subject prior to Visit 2. After eligibility is confirmed, the subject will be enrolled prior to Visit 2 and issued a subject number.

In consultation with their prescribing physician, any individuals taking psychiatric medications will start tapering off these medicines, allowing for a washout period of 5 times the half life of each medicine before Visit 2.

Subjects will receive a single open-label experimental session of MDMA-assisted psychotherapy with the full dose of MDMA. Procedures for MDMA-assisted psychotherapy will be as follows:

- a. On the day of the experimental session, the subject will arrive approximately 1-1.5 hours prior to drug administration.
- b. Confirm continuing eligibility by reviewing inclusion/exclusion criteria.
- c. Perform a urine drug screen. A positive drug screen will be reviewed by the investigator and may cause delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the subject from the study.
- d. If the subject is a female of childbearing potential, perform a urine pregnancy test. A positive pregnancy screen is a cause for withdrawal from the study.
- e. If the subject continues to meet the study criteria and reports that he/she followed appropriate rules and restrictions, the session will proceed.
- f. Review procedures for the experimental session with the subject.
- g. Record the entire session to video and audio. Subjects may receive a copy of audio or video recordings of their experimental session upon request.
- h. The session will last for approximately eight hours or longer, followed by an overnight stay at the study site.
- i. Administer the C-SSRS approximately one hour to a half hour prior to drug administration.

Table 4. Schedule of procedures and measures for the experimental session

Approximate Time	Procedure or Action
9:00	Urine drug screen and pregnancy test. Subject gets acclimated to the environment, C-SSRS
9:45	Baseline BP, Pulse, Subjective Units of Distress Rating (SUD), Body Temperature (BT)
10:00	MDMA Administration , begin recording to audio and video
10:30	BP, Pulse
11:00	BP, Pulse, SUD, BT
11:30	BP, Pulse; Can administer optional supplemental dose starting now
12:00	BP, Pulse, BT
12:30	BP, Pulse, SUD
13:00	BP, Pulse
13:30	BP, Pulse, BT
14:00	BP, Pulse, SUD
Every half-hour, and as needed	BP, Pulse
Every 60-90 minutes	SUD, BT
Approximately 6 hours after drug administration	C-SSRS, General Wellbeing

- j. Before drug administration, discuss and review the subject's goals, intentions and concerns and some of the commonly experienced effects of MDMA.
- k. Confirm that the subject has not used caffeine or nicotine 2 hours before and 6 hours after the drug administration.
- l. The subject's body temperature will be measured approximately 15 minutes prior to initial dose administration and approximately every 60 to 90 minutes after that. The investigators may take more frequent measurements if the body temperature exceeds more than 1°C above baseline.
- m. Subjects will complete the SUD prior to initial dose administration. Subjects will complete the SUD every 60 to 90 minutes after that, until the session is over, allowing a window of up to 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the investigators can make a greater number of measurements as their clinical judgment dictates.
- n. Measure blood pressure and pulse prior to the experimental session, and once every half-hour throughout the experimental session. More frequent measures will be taken if the investigators judge them to be medically indicated. Participants with controlled hypertension will have blood pressure and pulse assessed every 15 minutes for the first five hours and every 30 minutes for the next three hours. Blood pressure will also be measured more frequently if clinically significant symptoms are observed, such as chest pain, shortness of breath or neurological symptoms.
- o. At approximately 10:00 in the morning, subjects will receive the initial dose of drug

- along with a glass of water.
- p. The subject will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided if the subject wishes to use them. Subjects will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material [91-93]. Subjects may speak to the investigators whenever they wish, and the investigators will provide guidance and support as needed.
 - q. After the first hour, if the subject has not spoken spontaneously, check in with him/her about the nature of their experience. For the rest of the experience, as appropriate, the investigators will support and encourage the subject in emotional processing and resolution of whatever psychological material is emerging.
 - r. Record any spontaneously reported reactions during the session.
 - s. Provide water and electrolyte containing fluids throughout the session but not to exceed 3 L overall.
 - t. A supplemental dose half the size of the initial dose may be administered approximately 1.5 to 2.5 hours after the initial dose unless contraindicated by safety measures.
 - u. Provide food during the latter part of the session.
 - v. If there is a support individual who has previously been asked and has agreed to be present during part or all of the MDMA session, that person may arrive during the session at whatever time has been agreed upon, but will wait in the waiting room until brought back to the session room by one of the investigators. The support person may arrive after the session has ended.
 - w. If it is appropriate to do so, initiate the first question of the C-SSRS at any point in the session if the subject is experiencing significant psychological distress that does not respond readily to processing with the investigators according to the methods described in the MDMA-assisted psychotherapy treatment manual.
 - x. End the session if all medical and psychiatric parameters are acceptable and the subject is alert, ambulatory and emotionally stable.
 - y. The subject will complete the SOCQ in the interval after the end of the experimental session and prior to leaving the treatment facility the next day.
 - z. The investigators will depart the site when they have concluded that the subject is emotionally and medically stable. Investigators shall remain available to subjects during the experimental session and for one week after via 24-hour cellular phone.
 - aa. Spontaneously reported reactions, AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.

Subjects will remain overnight in an appropriately furnished room at the study site. With the approval of the investigators, a companion may accompany the subject during the overnight stay. An attendant will check in periodically on the subject during the overnight stay, even if a companion is present. The attendant will be an individual with some previous training in managing psychological distress. If there is an emergency or the subject needs additional support, the attendant can contact the investigators. The subject and a companion (if applicable) will receive information that will allow them to contact the investigators during the overnight stay in the case of an emergency or request for additional support. Subjects will be encouraged to use much of the time during their

overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

Benzodiazepines or zolpidem may be used if needed after the experimental session, as approved by the investigator.

5.2.4 Integrative Session 24 Hours after Experimental (Visits 3)

- a. On the morning after the experimental session, both of the investigators from the subject's team will meet with the subject during a 90-minute integrative therapy session.
- b. The entire integrative psychotherapy session will be recorded to audio and video. Subjects may receive copies of this session upon request.
- c. Administer the C-SSRS just prior to beginning of the integrative session.
- d. Discuss and review events that occurred with the subject during the experimental session, including thoughts, feelings and memories. If necessary, the investigators will help the subject to reduce any residual psychological distress he or she is experiencing. The investigators will also encourage the transfer of states of acceptance, feelings of intimacy, closeness and reduced fear experienced in the experimental session to emotionally threatening everyday situations. The investigators will be supportive, validating the experience and facilitating understanding and emotional clearing.
- e. The investigators will remain accessible any time the subject needs support outside the scheduled integrative session.
- f. Assess the subject's mental health and the presence of any remaining reactions during integrative psychotherapy immediately after the experimental session.
- g. The integrative psychotherapy session can also serve as an opportunity for the investigators to gather information about the effects of the drug on the subject in an unstructured manner.
- h. After the integrative psychotherapy session, a person previously selected by the subject will provide a ride home to the subject. If the subject is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the subject due to unforeseen events, the investigators will assist the subject in finding an alternative means of returning home.
- i. Spontaneously reported reactions, Adverse Events and Medications will be collected as described in Sections 8.5 and 9.0 of the protocol.
- j. Remind the subjects that they will have a daily contact with a therapist for the next 7 days.

5.2.5 Daily Telephone Contact for Seven days after the Experimental Session

- a. Starting on the day of the integrative psychotherapy session following the experimental session, one of the investigators will contact the subject via telephone or in person on a daily basis for one week.
- b. The integrative contact will be for a brief check-in lasting 5 to 15 minutes, or as long as necessary to address any of the subject's concerns and to assess the subject's well-being. Additional telephone contact can be initiated at the request

- of the investigators or the subject.
- c. On the second and the seventh day of contact after the experimental session, the subject will complete the C-SSRS.
- d. General wellbeing will be assessed at each phone call.
- e. Spontaneously reported reactions, AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.

5.2.6 Additional Integrative Psychotherapy Sessions (Visits 4 and 5)

- a. The subject will have two additional integrative psychotherapy sessions lasting approximately 90 minutes with both of the investigators from the subject's therapist team. The investigators may conduct more sessions if they and the subject deem it necessary.
- b. Record each integrative session to audio and video. Subjects may receive a copy of one or more integrative sessions upon request.
- c. The C-SSRS will be administered just prior to beginning of each integrative session.
- d. General wellbeing will be assessed at each integrative session.
- e. The subject and investigators will continue to work on supporting the subject as she or he considers his or her experiences during the experimental session.
- f. The investigators will use clinical judgment to assess the subject's psychological wellbeing during this period of time. If there are any indications of continuing anxiety or distress, the investigators may arrange to work on reducing the distress at a specially scheduled integrative therapy session, through continuing contact, or at the next regularly scheduled integrative therapy session. The subject may also initiate contact with the investigators at any time throughout the study.
- g. AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.
- h. If an integrative session falls within the period of telephone contact and additional phone call is not required that day, all things normally collected during the telephone call will be completed in person.

5.2.7 Evaluation Two Months after the Experimental Session (Visit 6)

This visit will consist of two meetings that may be completed on separate days, one with the independent rater and the other with the investigators at the study site.

- a. Subjects will meet the independent rater for approximately an hour and a half.
- b. The independent rater will administer:
 - CAPS to assess PTSD symptoms
 - PDS to assess self-reported PTSD symptoms
 - BDI-II to assess depression symptoms
 - GAF to assess general psychological function
- c. After completing all assessments and measures with the independent rater, the subject will meet with the investigators for approximately 60-90 minutes.
- d. The investigators will assess suicidality with the C-SSRS.

- e. General wellbeing will be assessed.
- f. Subjects will complete the Responses to Research Participation Questionnaire (RRPQ).
- g. Subjects will receive a memory aid card for use between this visit and the 12-month follow up. Subjects will use this card to record any AEs related to their psychiatric status, any changes in their psychiatric status and any medications taken to treat these AEs during the follow-up period. Subjects will be asked about these at the termination visit. Memory aids will not be collected.
- h. AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.

5.2.8 Long-Term Follow-up at Twelve Months

The subjects will be evaluated for long-term effects 12 months after their MDMA-assisted psychotherapy session. This visit will consist of two meetings, one with the independent rater and the other with the investigators. The meetings may take place at the study site or over the telephone.

- a. The independent rater will administer the CAPS, PDS, BDI-II and GAF.
- b. Subjects will have a final meeting with at least one of the investigators to review specified AEs and medications since the last visit. Subjects should bring the memory aid cards to this visit, to be used as aids in recollection. These cards will not be collected. Information on AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.
- c. The investigators will assess suicidality with the C-SSRS.
- d. General wellbeing will be assessed.
- e. Subjects will complete a questionnaire assessing positive and negative long-term effects of the study.
- f. Subjects will complete the termination visit at this time.

5.3 Subject Numbering

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "01". Subjects who meet all inclusion and no exclusion criteria will be enrolled into the study and will be assigned a five-digit subject number. The first two digits will be "E2" to identify the protocol number. The last two digits will identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be E201, the second E202, etc. In total, up to three subjects will be enrolled into the study.

5.4 Removal or Withdrawal of Subjects from the Study

Subjects can withdraw consent at any time without prejudice. The investigators can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with elements of the experimental session and related visits that are critical for safety. If the investigators withdraw a subject from the session, the investigators will explain the reason for withdrawing the subject.

If a subject develops any exclusion criteria that, in the opinion of the Medical Monitor, affect the safety of the subject, including psychiatric diagnosis, pregnancy or excluded medications, the subject may be removed from the study. Subjects who withdraw from the study will not be replaced.

Subjects will be clinically monitored after withdrawal by at least one of the investigators, the cause of which will be recorded in the subject's source records and CRF. Whenever possible, the tests and evaluations listed for the termination and evaluation visits will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the therapist and/or the Sponsor.

5.5 Premature Discontinuation of the Study

The Sponsor or the clinical investigator (following a consultation with the Sponsor) has the right to discontinue this study at any time. If the study is prematurely terminated, the investigator should promptly inform the study subjects and assure appropriate therapy and follow-up. All procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the Sponsor and will be treated in accordance with federal and local regulations.

6.0 Investigational Product

6.1 Description

The investigational product to be used in this research protocol is MDMA. This ring-substituted phenylisopropylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor [94-96]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower.

6.2 Administration

The study will consist of an open-label administration of a full dose of MDMA (125 mg) possibly followed by a supplemental dose of 62.5 mg, unless contraindicated based on safety measures.

6.2.1 Preparation

The investigational product that will be used in this study is MDMA HCl manufactured by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University in 1985. MDMA in bulk will be sent by Dr. David Nichols Ph.D. or his representatives at Purdue University, in West Lafayette IN, to the Clinical Investigator, who has been issued the Schedule 1 license by the Drug Enforcement Agency (DEA). MDMA will be compounded by the appropriate pharmacist, weighed, and placed into gelatin capsules of 125 mg for the initial dose and 62.5 mg for the supplemental dose.

6.2.2 Labeling

During compounding, each dose of MDMA will be placed into a holding box (See sample holding box label).

The initial and supplemental doses of MDMA for a single subject to complete the experimental session will be stored in an envelope labeled with the protocol number, drug name, lot number, unique envelope number, Sponsor name and a statement that the drug is for clinical trial use only (see envelope label). Each dose of MDMA will be labeled and stored in the individual container within the envelope (see container labels for each session and dose). Labels will be provided by the Sponsor and applied by the pharmacist. All drug labels will comply with federal, state and local regulations.

Holding Box Label
MAPS Study # MP1-E2 Investigational Product: MDMA Initial Dose: 125mg Lot #: 5810-09 Administer as per protocol Caution-Limited by Law to Investigational Use Only

Envelope Label
MAPS Study # MP1-E2 Investigational Product: MDMA Dose: 125 mg, 62.5 mg Lot #: 5810-09 Envelope #: XXXX Subject # _____ Administer as per protocol Caution-Limited by Law to Investigational Use Only

Container label
MAPS Study # MP1-E2 Lot #: 5810-09 Dose: 125 mg MDMA Envelope #: XXXX Subject # _____ Administer as per protocol Investigational Use Only

Container label
MAPS Study # MP1-E2 Lot #: 5810-09 Dose: 62.5 mg MDMA Envelope #: XXXX Subject # _____ Administer as per protocol Investigational Use Only

Each dose will consist of the specified amount of racemic MDMA. Initial doses will be distinguished from supplemental doses through labeling “Dose: 125mg” and “Dose: 62.5 mg” to ensure that the correct dose is administered at the scheduled time. Each dose of MDMA will be administered along with a glass of water or electrolyte-containing fluid.

6.3 Drug Accountability

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

6.4 Drug Storage and Handling

MDMA is a Schedule 1 compound and will be stored and handled in compliance with all relevant local and federal regulations. In accordance with the DEA requirements, the Clinical Investigator will be responsible for storing and dispensing the MDMA. It will be stored in a safe mounted to the floor that has been inspected and approved by the DEA for this purpose. Only the Clinical Investigator with the Schedule 1 license will know the combination to the safe. The room in which the safe is mounted has an alarm system and will be locked whenever the investigator or his staff are not present.

Investigational product will only be removed from the safe for one subject at a time at the time of the session, and the MDMA will not leave the premises. All doses administered will be recorded on the appropriate accountability logs.

Records pertaining to the use of this Schedule 1 compound will be maintained in accordance with relevant federal and state regulations. They will be kept separately from other records and will be maintained in a locked cabinet in a locked office with an alarm system.

6.5 MDMA Stability

As described in Section 6.2.1, MDMA used in this study was prepared for human consumption in 1985 by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University. Complete details on the chemistry, manufacturing and control of the MDMA to be used are described in Drug Master File (DMF) # 6293. 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 prior to starting MAPS' first U.S. pilot study of MDMA-assisted psychotherapy in people with PTSD. The analysis found the MDMA to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart on February, 2006, continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9% pure. This MDMA was used in an investigation of MDMA-assisted psychotherapy that took place in the U.S. with drug administration ending in 2008, and it was also used in non-sponsor supported study in 2006 [97].

7.0 Risks of Participation

7.1 Risks and Discomforts Associated with Non-drug and Experimental Psychotherapy Sessions and Assessment of Measures

During screening, non-drug and drug-assisted psychotherapy sessions and assessment of study measures, subjects will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the

effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy, experimental and open label sessions. Psychotherapy is 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 will be recorded to audio and video. Subjects may feel uncomfortable with having their sessions recorded. Subjects may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment. Subjects will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

7.2 Risks of Receiving MDMA

Spontaneously reported reactions and common adverse effects of MDMA are known to be modest and have generally not been associated with serious discomfort by healthy volunteers in previous studies. Spontaneously reported reactions are compiled from previously published literature and include anxiety, diarrhea, difficulty concentrating, dizziness, drowsiness, dry mouth, fatigue, headache, impaired gait/balance, increased irritability, rumination (increased private worries), insomnia, jaw clenching, tight jaw, lack of appetite, low mood, muscle tension, nausea, nystagmus, parasthesias, perspiration, restlessness, sensitivity to cold, thirst and weakness. In MAPS study MP-1 (N=23), comparing MDMA-assisted psychotherapy to inactive placebo, anxiety, headache, fatigue, insomnia and lack of appetite were spontaneously reported by 40% to 80% of participants in both the MDMA and placebo conditions. However, 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 Investigator's Brochure.

MDMA may produce mild alterations in sensory perception and altered perception of time [52, 74, 98]. Women may be more sensitive to these effects [75]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change while driving [58]. For this reason, subjects 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.

Further information on the risks associated with MDMA, including information drawn from case reports and studies of Ecstasy users, can be found in the Investigator's Brochure.

7.2.1 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 six hours. In less than 5% of volunteers in Phase 1 studies, increases in blood pressure 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 Investigator's Brochure.

Risks posed by elevated blood pressure will be addressed by excluding people with hypertension, unless it is well-controlled, as described in Exclusion criteria section 4.2.2, and by monitoring blood pressure and pulse as described in Safety Measures section 5.1.2. During the experimental session the investigators will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or another cardiovascular emergency. Subjects reporting chest pain, shortness of breath or neurological symptoms or other potential indicators of hypertension that may need intervention will have more frequent measurements.

Reasons for moving a patient to an emergency department or ICU would include, but not be limited to, severe headache in the setting of hypertension, angina or neurological deficits regardless of blood pressure. In case of an emergency, intravenous anti-hypertensive agents will be available in addition to the usual resuscitation drugs and equipment. The investigators may, at any time, make a clinical judgment to transfer the patient to the ICU for closer monitoring and additional treatment.

The investigators will be prepared to respond to rare complications of cardiovascular effects, such as stroke or myocardial infarction. The investigators 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. If any participant has neurological deficits, whether or not they are associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as described above. He or she will be transported to the emergency department at East Cooper Medical Center, the nearest hospital, for a head CT scan and 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 [99, 100].

The investigators will observe the participant and note any complaints of chest pain. If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will undergo a stat ECG, receive oxygen and an IV and will be monitored as described above. If necessary, he or she will be transported to ICU or a location in the hospital where appropriate care can be given. He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the participant has had an acute myocardial infarction (AMI), he or she 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 [101].

7.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported 1–3 days after the MDMA administration [47, 75, and see the IB]. 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 experimental session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following the MDMA session as a result of subjects 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, and have responded well to reassurance from the investigators, with occasional use of benzodiazepines for anxiety. In this study, subjects will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties subjects might have with acute or sub-acute reactions. All study participants will have undergone previous MDMA-assisted psychotherapy sessions and will be familiar with the experience. The potential for destabilizing psychological distress will be minimized by:

- excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders)
- a preparatory non-drug psychotherapy session before the experimental session
- creating an atmosphere of trust during the experimental session
- close monitoring
- daily contact with subjects for the period of a week after the experimental session
- providing non-drug integrative psychotherapy sessions
- Subjects will remain at the study site for the night after the experimental session to further reduce psychological distress. Qualified personnel will be available during the overnight stay to respond to the needs of the subject. Attendants will be instructed to contact the investigators upon request or at the appearance of signs of a potential serious adverse event.

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

At the end of the 6–8 hour experimental session, if the subject is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

- If the subject is anxious, agitated, in danger of any self-harm or is suicidal at the end of the experimental session, the investigators will remain with the subject for at least two more hours. During this time, the investigators will employ affect management techniques, will talk with the subject to help him or her gain cognitive perspective of their experiences, and will help them implement the self-soothing and stress inoculation techniques presented during the preparatory session. If this situation should occur during an integrative therapy session, at least one of the investigators will be available to stay with the subject for at least two additional hours.
- If a subject remains severely anxious, agitated or in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period, the clinical investigator will decide between the following options:
 1. A psychiatric nurse, therapeutic assistant or therapist will stay with the subject until the time of his or her appointment with the investigators the next day. The investigators will then meet with the subject daily until the period of destabilization has passed.
 2. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an MDMA session, the investigators may prescribe a benzodiazepine or zolpidem as a “rescue medication.” This medication will be captured on the concomitant medications CRF page. Investigators should not prescribe an SSRI, SNRI or MAOI in this context. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.
 3. Hospitalization for stabilization. Should a subject remain psychiatrically unstable despite the above measures he or she will be transferred to a psychiatric inpatient unit.

Subjects hospitalized after becoming psychiatrically unstable will be suspended from the protocol until after recovery or stabilization, at which time the investigator will carefully evaluate the subject’s emotional status.

For those subjects engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the subject's outside therapists will be involved in the management of any psychiatric complications.

7.2.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [75], and ambient temperature does not enhance or attenuate this slight elevation in humans.

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, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, ice packs will be used, blood will be drawn for stat CBC, electrolytes, BUN/creatinine, glucose, CPK, PT, PTT, platelets and liver enzymes, and urine will be collected for urinalysis.

7.2.4 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 (often used along with other drugs) during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [102, 103], as discussed in the Investigator's Brochure.

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 the experimental session and must agree to use birth control for the duration of the study.

7.2.5 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [104]. However, they are basing their case on studies that employed inappropriately high doses of MDMA utilized in animal studies, and on human studies comparing the effects of repeated use of ecstasy, often along with other drugs. We have carefully considered the risks of such neurotoxicity and concluded that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. More information on the potential neurotoxicity of MDMA can be found in the Investigator's Brochure.

7.2.6 Risk Mitigation

Prior to participating in the current study, all study subjects will have undergone the Sponsor initiated MP-1 study, which included two to three MDMA-assisted psychotherapy sessions, and are known to have tolerated MDMA well. Careful review of

medical records and screening data will be utilized to exclude potential participants with preexisting exclusionary medical conditions from the study. Study procedures have been developed to mitigate the risks of receiving MDMA described in detail in the Investigator's Brochure. Ambient temperature will be kept at a comfortable level during the experimental session. Subjects will not be allowed to drink more than 3L 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.

7.3 Abuse Liability

Findings in humans and nonhuman 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 provided in the Investigator's Brochure

Whether or not MDMA's abuse potential will negatively affect people with PTSD exposed to MDMA when given along with psychotherapy is an open question for which there is of yet no direct data. Mithoefer and colleagues are in the process of analyzing data from a long-term follow-up of participants in their study of MDMA-assisted psychotherapy. Only one of 20 participants took Ecstasy on one occasion after completing the study and failed to reproduce the experience she had had with the therapists during the study, and a number of participants volunteered that they would never seek out Ecstasy outside a legal, controlled therapeutic setting.

Diversion is not an issue in this protocol because MDMA will only be administered a few times under the supervision of the clinical investigator 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 adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Investigator's Brochure or an event that 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 identified. If an AE is unresolved at the conclusion of the protocol, a

clinical assessment will be made by the investigator and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” CRF will be determined by the investigator 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 investigator based on the following definitions:

1. Not Related

The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject’s pre-existing condition.

2. 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.

The relationship of the study treatment to an AE will be determined by the investigator.

8.2 Spontaneously Reported Reactions

Commonly expected spontaneously reported reactions are collected on a separate CRF page and will be categorized as mild, moderate or severe. Spontaneously reported reactions are compiled from previously published literature and sponsor-supported investigations and include anxiety, diarrhea, difficulty concentrating, dizziness, drowsiness, dry mouth, fatigue, headache, impaired gait/balance, increased irritability, rumination (increased private worries), insomnia, jaw clenching, tight jaw, lack of appetite, low mood, muscle tension, nausea, nystagmus, parasthesias, perspiration, restlessness, sensitivity to cold, thirst and weakness. Spontaneously reported reactions will be collected during the experimental session and the seven days of telephone contact following the integrative session that occurs on the day after the experimental session.

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

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

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

8.4 Medical Emergencies

The preparatory session, MDMA session and integrative sessions will be conducted in the psychiatric offices of the investigators. The offices are located 2.6 miles from the nearest emergency room. The office will be equipped with a "crash cart" containing the emergency medications and equipment necessary to respond to any complications. Intravenous fluids, antiarrhythmic drugs, antihypertensive drugs (such as nitroprusside and labetalol), injectable epinephrine and other pressor agents, and other standard emergency drugs and equipment will be available on-site as a means of treating any potential allergic reactions or other medical emergencies. In addition to drugs, the crash cart will contain a defibrillator (with rhythm monitoring capability), an oxygen tank, a suction device, a pulse oximeter, an IVAC pump and intubation equipment (including laryngoscope, and endotracheal tubes). As is now common practice in emergency departments, an automatic blood pressure cuff will be used in place of intraarterial blood pressure monitoring equipment. In the unlikely event of cardiac arrest, the investigators will follow the American Heart Association guidelines for 2-person BLS for Healthcare Providers (including defibrillation with an automated external defibrillator (AED) until the arrival of Emergency Medical Services (EMS), at which time Advanced Cardiac Life Support (ACLS) procedures will be instituted. With these personnel and equipment, the researchers, in conjunction with EMS if necessary, would be able to begin treatment in the office and then transport the participant by ambulance, if hospital admission were required, to the emergency department or ICU at East Cooper Medical Center, the nearest hospital.

8.5 Adverse Event Collection

All SAEs will be collected for the duration of the protocol. 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 to the Sponsor within 24 hours of the investigator's awareness of their occurrence. All SAE reports should be faxed to the Sponsor. A fax number will be provided to the site in separate site-specific instruction for SAE reporting. In addition to the fax, the Clinical Investigator (CI) or designee should call the CRA during normal working hours and verbally inform the CRA of the SAE. During off hours or if medical advice is needed immediately, please call the Sponsor Medical Monitor. Instructions for SAE reporting with all contact numbers will be provided to the site prior to study start.

Medical Monitor

Julie Holland MD
NYU School of Medicine
200 East 33rd Street, Suite 16H
New York, NY 10016
Voice mail: 212-358-5808

Study Monitor contact information will be provided in a separate contact list.

Adverse events that will be collected for the duration of the protocol are:

- All SAEs will be collected through termination.
- All Adverse Events and spontaneously reported reactions will be collected on the day of drug administration and for seven days after the experimental session.
- Events requiring medical attention will be collected from the experimental session through the 12-month follow up.
- 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.
- Any Adverse Event leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

As described in Section 5.2.7, subjects will receive a memory aid card for use between the 2-month and 12-month follow-up visits to record any AEs related to their psychiatric status during this follow-up period.

9.0 Concomitant Medications and Tapering Instructions

Concomitant medications will be recorded during screening. If the subject is being treated with psychiatric drugs at the time he or she is recruited into the study, the prospective subject will be encouraged to discuss any medication tapering necessary with his or her outside treating physician, and will be required to give the investigators permission to do so as well. The drugs will then be tapered off in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life).

The investigators will request information about any changes in medication just prior to the experimental session. All medications, over the counter (OTC) and prescription, will be collected from screening through 7 days after the MDMA session. From 7 days after the MDMA session through study termination only prescription or OTC medications taken to treat AEs, as specified in Section 8.5, and all changes including discontinuations or additions to psychiatric medications will be collected. Medications will be recorded on the concomitant medications CRF.

Subjects must be willing to refrain from taking any psychiatric medications, including stimulants, from 5 half-lives before the MDMA session until 10 days after the MDMA session, with the exception of gabapentin when prescribed for pain control. After that subjects may resume taking psychiatric medications taken at baseline at the discretion of the prescribing physician, but no new psychiatric medications may be added until after the 2 month follow-up.

Subjects may receive a designated rescue medication that may be administered in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual). Rescue medications may be benzodiazepines, as lorazepam, or zolpidem. SSRIs, SNRIs and MAOIs should not be used as rescue medications.

Subjects must agree that, for one week preceding the MDMA session:

- a. They will refrain from taking any herbal supplements (except with prior approval of the research team).
- b. They will refrain from taking any prescription or nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs, acetaminophen, birth control pills, thyroid hormones, or other medications approved by the research team).

As described in Section 5.2.7, subjects will receive a memory aid card for use between the 2-month and 12-month follow-up visits to record any changes in medications used to treat AEs related to their psychiatric status during this follow-up period.

10.0 Clinical Laboratory Assessments

The clinical investigator or the study staff will examine laboratory assessments gathered as a part of screening for assessing participant eligibility. The following laboratory assessments will be performed at screening and immediately before the experimental session:

- A urine-dip pregnancy test for females of childbearing potential
- Urine drug screening test

The urinary pregnancy tests and drug tests will be performed at the study site. Hepatitis serology or other additional clinical tests may be conducted as indicated to determine the subject's eligibility for the study.

11.0 Study Monitoring, Auditing and Documentation

The clinical investigators and the study staff will be trained prior to the start of the study. The study site will be monitored by site visits and telephone calls to the investigator by representatives of the Sponsor. The site will be monitored as appropriate for the rate of enrollment in order to comply with GCP guidelines and to ensure validity of the study data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the Sponsor will be completed for each subject enrolled.

During or after the study, the regulatory authorities, the IRB, and/or representatives of the Sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

12.0 Data Analysis

The sponsor will collect outcome and safety measures from all subjects who enroll in and complete this study. This will include CAPS subscale, global and diagnostic scores, PDS severity scores, BDI-II scores, and GAF scores. The sponsor will also collect SOCQ subscale scores, vital signs, SUD scores and spontaneously reported reactions. Data will be examined informally and descriptive statistics will be computed. Simple tests of differences between baseline and follow up medians or means will be employed as described below.

The sponsor will compute difference scores for Global CAPS, PDS severity, BDI-II and GAF scores at baseline (upon enrollment in this study) and two months after the experimental session, and scores at baseline and at 12-month follow up. After difference scores are computed, the sponsor will observe the degree to which scores are greater than zero, indicating improvement at the second time point,

The Sponsor will correlate each SOCQ score with CAPS at 2-month and at 12-month follow-up to determine whether one or more facet of the experience during the MDMA-assisted session was related to symptomatic reduction.

There is no expectation that conditions will differ in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, such as depression. Also, participants in this study will all be Caucasian and are likely to be female given that the majority of the original sample were women. However, owing to a small sample size, such variations may arise by chance.

The investigators will record average baseline and post-drug peak blood pressure, heart rate and body temperature for participants during the experimental session. The investigators will also record spontaneously reported reactions and AEs as described in section 8.5. Descriptive statistics will be computed for vital signs and subjective distress during the experimental session. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

12.1 Statistical Power

This is a proof-of-principle study. The study is underpowered for detection of differences within subjects over time of a small or moderate effect size, and it may detect differences if the effect size is large. Although a power analysis has been provided, such analyses are generally performed for tests where formal analyses will be applied to the data.

Analyses of MAPS' completed U.S. study of MDMA-assisted psychotherapy in 20 people with PTSD found an effect size of 1.24 for treatment efficacy, as represented by changes in CAPS score [2]. The effect size was for a between-subjects study. The estimated effect size for this study may be lower as a result of a small sample size. Also, participants are selected on the basis of increasing PTSD symptoms. Using Lenth's software [105] and assuming that there will be data from three subjects, the paired t-test was used to calculate the effect size. If the true difference between the previous measure

of PTSD and the next is 0.7, then power = 0.12, and if the difference is 1, then power may be 0.18.

13.0 Ethics

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

The protocol and the proposed informed consent form (ICF) must be reviewed and approved by an Independent Review Board (IRB) before the study start. Signed and dated documentation that the protocol and informed consent have been approved by the IRB must be provided to the Sponsor. Prior to study start, the Clinical Investigator is 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 investigators are responsible for obtaining informed consent in adherence to Good Clinical Practices (GCP) and according to applicable regulations prior to entering the subject into the trial. Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The informed consent should include access to original medical records and processing of coded personal information. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the MDMA session and to consider participation.

The process of obtaining informed consent should be documented in the subject source documents.

The investigators will provide a copy of the signed ICF to the subject, and will maintain the original in the investigator site file (ISF).

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICFs and other written information should receive approval from the IRB before use.

The subject should be informed in a timely manner if new information becomes available that may affect the decision to take part in the study. The communication of this information should be documented.

Participants can withdraw consent for participation in the study at any time without prejudice. If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, MAPS will have full access to the subject'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 study participants in their role as research subjects. Despite this, absolute privacy cannot be guaranteed. Data collected from each subject will be identified only by the subject's initials and by a subject number on the source documents. All study measures, records, and audio and video recordings will be kept in a locked file drawer in a locked office. Access to study measures will be limited to regulatory agencies, researchers assessing the subject for changes in symptoms, Sponsor representatives, and individuals analyzing data. Researchers with access to data will not be provided with any information that would identify subjects by name or by other means.

Removing identifying information from data and restricting access to researchers directly involved in assessing the subjects 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.

All psychotherapy sessions will be recorded to video and audio. These recordings will be used for the treatment manual development and potentially for training therapists to perform MDMA-assisted therapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. Confidentiality of subject names and addresses will be maintained in these recordings. Full names and addresses will not appear in these recordings.

16.0 Costs to Participants

The Sponsor of this study will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions, for the psychological and laboratory testing, for the study drug and for any rescue medications used during the study. The subject and their health insurance (if any) will not be charged for any procedures done solely for the purpose of the study.

The subject or their health insurance remains responsible for the ongoing treatment unrelated to the study. The Sponsor will not cover medical expenses related to injuries, which occur during the study period that are not directly related to study procedures.

17.0 Treatment and Compensation for Study Related Injury

In the event of a study-related injury, the Sponsor will cover any costs that arise from treating the injury. The Sponsor has an insurance policy to cover the subjects from any disabilities resulting from the study procedures. The subject will be compensated according to the level of disability arising from medication or procedures used in the study. This insurance coverage protects the Sponsor, the institution and the investigators from any legal actions pursued against them.

18.0 Record Retention

Investigators must retain all study records required by the Sponsor and the applicable regulations in a secure and safe facility. The investigator must consult a representative of the Sponsor before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to the applicable regulations in the ISF. 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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