

**PROTOCOL MP-8**

**IND #63,384**

**December 17, 2009**

**A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of  
MDMA in Conjunction with Manualized Psychotherapy in 16 Veterans with  
Chronic Posttraumatic Stress Disorder (PTSD)**

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## 1.0 List of Abbreviations

ACLS	Advanced cardiac life support
AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI	Beck Depression Inventory
BLS	Basic Life Support
C	Celsius
CAPS	Clinician Administered PTSD Scale
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPCL	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
LSD	d-lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
NK	Natural Killer
OTC	Over the counter (non-prescription)
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTGI-C	Post Traumatic Growth Inventory-Current state
PTSD	Posttraumatic Stress Disorder

PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
RCT	Randomized clinical trial
RRPQ	Reactions to Research Participation Questionnaire
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for Diagnoses
SERT	Serotonin Transporter
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

## **2.0 Background Information**

### **2.1 Introduction**

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with posttraumatic stress disorder (PTSD).

Encouraging data has been obtained and submitted to the FDA from MAPS' recently completed United States (U.S.) pilot study, IND #63-384 (MP1). MAPS is currently sponsoring other Phase 2 studies in Switzerland and Israel. An additional Phase 2 study is planned to start in the near future in Canada, with approval from Health Canada and a Canadian IRB already obtained. Ongoing and planned Phase 2 studies, along with the study described in this protocol, are laying the groundwork for an eventual End-of-Phase 2 meeting with FDA and possible Phase 3 multi-site MDMA/PTSD research studies.

The proposed pilot study will examine the safety and efficacy of MDMA-assisted psychotherapy in sixteen veterans with war-related PTSD, and will seek to enroll roughly equal numbers of men and women. Since many veterans with PTSD have not been offered and/or have declined medication or psychotherapy for their PTSD, this study will include veterans with chronic PTSD of at least six months duration, but not necessarily treatment-resistant PTSD.

MAPS' initial US pilot study enrolled 21 subjects, a majority (17) of whom were women suffering from PTSD related to sexual assault and/or childhood sexual abuse. Only two subjects had PTSD from war-related trauma (US veterans of the Iraq War) and both were male. According to the European Medicines Agency (EMA) Guideline for the Development of Medicinal Products for the Treatment of Post-Traumatic Stress Disorder (PTSD), it is desirable to examine treatment response in homogenous samples, conducting separate trials for different populations. The findings from this proposed study in veterans with war-related trauma will be compared with results from our initial US pilot study, mostly in women survivors of sexual abuse and assault.

In order to refine our double-blind methodology, the proposed study will also evaluate three different doses of MDMA to determine their relative success in achieving blinding of co-therapists, subjects, and independent raters.

In addition, this will be the first study of MDMA-assisted psychotherapy to permit the enrollment of subjects with two medical conditions that were exclusion criteria in the previous trial; Hepatitis-C, and controlled hypertension. Should any subjects with these conditions seek enrollment in the study, they will be required to go through additional specified screening procedures and additional monitoring for safety during the experimental sessions.

A comprehensive review of the published, peer-reviewed MDMA research literature is contained in the Investigator's Brochure supplied by the sponsor. This document should be reviewed by the investigator prior to initiating the protocol.

## **2.2 Protocol Purpose**

## **2.3 Supporting Information**

### **2.3.1 Posttraumatic Stress Disorder**

PTSD is a serious, worldwide public health problem for which a wider array of effective treatments is needed. In the U.S., the lifetime prevalence of PTSD in the general population is between 6 and 10% [1]. Combat exposure can produce a form of PTSD that is "chronic, disabling and highly comorbid." [2, 3], and that it can be especially resistant to pharmacotherapy with Selective Serotonin Reuptake Inhibitors (SSRIs) [4]. PTSD is common in other countries as well [5-9]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [10], and it is estimated that the number of service members returning home with PTSD will be between 75,000 and 225,000 [11]. In 2004, the U.S. Veterans Administration spent \$4.3 billion on PTSD disability payments to approximately 215,000 veterans, most of them from the Vietnam War [12]. Due to the Iraq and Afghanistan wars, the number of veterans disabled by PTSD, and the cost of providing disability payments, has increased substantially since 2004. In countries where there is endemic armed conflict, the incidence of PTSD in civilians is often far greater [13-15]. PTSD is typically a chronic illness [16, 17], associated with high rates of psychiatric and medical co-morbidity, disability, suffering and suicide [7, 16, 18, 19]. During a recent appearance at a gathering of mental health professionals on October 26, 2009, US Secretary of Defense Robert Gates stated that "Beyond waging the wars we are in, treatment of our wounded, their continuing care, and eventual reintegration into everyday life is my highest priority,..I consider this a solemn pact between those who have suffered and the nation that owes them its eternal gratitude." [20]

An array of psychotherapeutic options exists for treating PTSD and two SSRIs (sertraline and paroxetine) are approved as PTSD treatments by the FDA. However, a significant minority of PTSD patients fail to respond adequately to established PTSD psychotherapies [21, 22], or respond in ways that are statistically significant but clinically inadequate. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [23]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

There is limited data about whether or not patients with war related PTSD are more difficult to treat than those with PTSD from other causes. A recent comprehensive review stated that, "Most, but not all, randomized clinical trials (RCTs) with combat (mostly Vietnam War) veterans showed less treatment efficacy than RCTs with nonveterans whose PTSD was related to other traumatic experiences.... Therefore some

experts believe that combat veterans with PTSD are less responsive than survivors of other traumas to treatment. Such a conclusion is premature. ... More clinical trials with combat veterans would be important and welcome additions to this literature” [24].

In recent years, there has been growing research into drugs or other methods that may augment the effectiveness of psychotherapy for PTSD. Examples of this are virtual reality-assisted exposure therapy [25, 26], and D-Cycloserine-assisted psychotherapy [27]. MDMA-assisted psychotherapy is another such approach that is being rigorously tested.

### **2.3.2 MDMA-Assisted Psychotherapy for PTSD**

To date psychotherapy has been the mainstay of treatment for PTSD and has a larger effect size than that of psychopharmacologic treatment. 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 proved to be effective in treating some aspects of PTSD symptoms [28]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [29]. However, a recent meta-analysis concluded that all “bona fide” psychotherapies, including all those listed above, are similarly effective for PTSD and had an average effect size of 0.25 [30].

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with a pharmacological adjunct intended to amplify and enhance particular aspects of psychotherapy. MDMA possesses unique pharmacological and psychological properties that may make it especially well suited for use as an adjunct to psychotherapy with PTSD patients [31-35]. This treatment consists of several administrations of MDMA-assisted psychotherapy within the context of a time limited course of non-drug psychotherapy over three to four months. MDMA-assisted psychotherapy is hypothesized to reduce symptoms from all three symptom clusters experienced by individuals diagnosed with PTSD; re-experiencing, hyperarousal and avoidance.

Anecdotal accounts, data from MAPS’ recently completed US clinical trial, and preliminary data from MAPS’ Swiss MDMA/PTSD study, all suggest that MDMA may provide unique benefits to people with PTSD when administered in combination with psychotherapy. It may assist people in confronting memories, thoughts and feelings related to the trauma without increasing either fear or avoidance in response to this confrontation. An increase in self-acceptance and increased feelings of closeness to others may also assist people with PTSD in forming a therapeutic alliance with psychotherapists.

Treatment goals for PTSD include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. One approach is to discover drugs that directly counteract these neurobiological changes. Paroxetine (Paxil)



and sertraline (Zoloft) are the only two drugs approved by the FDA in the US for treating PTSD, and are known to act largely via serotonin reuptake inhibition.. They may also block the down-regulation of brain-derived neurotrophic factor, but it is not known whether it can arrest and reverse the hippocampal atrophy found in PTSD patients [36]. Another approach to treatment of PTSD is to develop drugs and/or psychotherapeutic treatments that will indirectly interrupt the destructive neurobiological changes by decreasing or eliminating the stress reactions to triggers and the chronic hyperarousal of PTSD. 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 re-enforce 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 [37]. 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 [38, 39].

#### **2.4 Previous MDMA Research**

To date, MDMA has been administered to approximately 470 research participants, in both Phase 1 and Phase 2 studies, without any occurrences of drug-related Serious Adverse Events (SAEs) [40-54].

The highest initial and supplemental doses to be used in this study are 125 mg and 62.5 mg respectively), the same doses used in previous or ongoing studies taking place in the US, Switzerland and Israel. The lowest initial and supplemental doses (30 and 15 mg) are only five milligrams above the 25 mg dose used in some of these studies. Researchers have administered 75 mg of MDMA in a number of studies, including a study of MDMA-assisted psychotherapy in people with PTSD in Spain [55] and a series of basic research studies occurring in the Netherlands [e.g. 48, 56]. The addition of a supplemental dose half the size of the initial 75 mg dose produces a total dose (115 mg), below that used in the first US investigation of MDMA-assisted psychotherapy. The psychotherapy will be performed by the same pair of investigators who have conducted MAPS' first U.S. study of MDMA-assisted psychotherapy in people with PTSD, and they will conduct the same form of psychotherapy in this study.

#### **3.0 Protocol Objectives**

The objective of this pilot study is to explore the safety and estimate the effect size of efficacy for MDMA-assisted psychotherapy in veterans with PTSD, a group with a different index trauma from most subjects in prior investigations of this experimental treatment.

### **3.1 Primary Objective**

- Estimate changes in PTSD symptoms in people receiving each of three doses of MDMA, as measured via Clinician-Administered PTSD Scale (CAPS) score in Stage 1.

### **3.2 Secondary Objectives**

- Estimate changes in post traumatic growth in people receiving each dose of MDMA via PTGI-C scores in Stage 1.
- Estimate changes in quality of life via Global Assessment of Functioning (GAF) in participants in Stage 1 in active placebo, medium-dose and full-dose conditions.
- Estimate changes in symptoms of depression in participants in Stage 1 in all three dose conditions via BDI scores.
- Estimate PTSD symptoms through CAPS, post traumatic growth via PTGI-C, depression symptoms via BDI, quality of life via GAF before and after enrollment in all participants enrolled in Stage 2, the open-label study segment, before and after enrollment.
- Estimate PTSD symptoms via CAPS, post traumatic growth via PTGI-C, depression symptoms via BDI and quality of life via GAF one year after the third experimental session for each participant who received the full-dose condition in Stage 1 or who didn't enroll in Stage 2 after receiving either medium or active placebo doses in Stage 1, or one year after each participant enrolled in Stage 2 has completed the third open-label experimental session.
- Estimate the ability of the investigators and participants to accurately guess condition assignment when asked after to do so after each experimental session.

### **3.3 Safety Objective**

To monitor and ensure safety in participants enrolled in the active placebo, medium-dose and full dose conditions by assessing physiological effects, psychological distress, spontaneously reported side effects and suicidality.

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-CSSRS) during and after experimental sessions and on selected days of telephone or face to face contact. The same schedule of assessment will be employed during Stage 2.
- Quality of life, as assessed via Global Assessment of Functioning (GAF) will be performed by the independent rater at the same point in time as CAPS administration. Scores will be compared between active placebo, medium-dose and full dose conditions, both during Stage 1 and Stage 2.
- Subjective Units of Distress (SUDS) and vital signs (blood pressure, heart rate and temperature) will be measured during each experimental session, and comparisons will be made for SUDS and vital signs between active placebo, medium-dose and full-dose conditions.

- Adverse events and side effects will be collected during and after each experimental session. All serious adverse events (SAEs) and adverse events of concern to the participant will be collected throughout the protocol.

#### **4.0 Investigational Product**

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. More information on this produce is contained in Section 4.6 below.

#### **4.1 MDMA Activity Related to Proposed Action**

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [57, 58]. In the first completed study of MDMA-assisted psychotherapy in people with PTSD, the Principal Investigator of this protocol reported reduction in PTSD symptoms, as assessed by an independent rater, in people who received MDMA with psychotherapy instead of placebo and the same psychotherapy [49]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion [59-66]. Effects in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with Ecstasy (see for example [59] versus [67]). An increase in positive mood, increased access to emotionally intense material, increased interpersonal trust and compassion for the self and others, and anxiolysis likely all contribute to the therapeutic effects of MDMA. It is significant that MDMA reduces anxiety without depressing the sensorium or inhibiting patients capacity to experience and reflect upon intense emotions. Increased interpersonal closeness may permit patients to explore upsetting thoughts, memories or feelings. Facilitated recall and unusual and potentially innovative shifts in thinking and perception may contribute to generating new perspectives about past or current thoughts, feelings and experiences.

#### **4.2 MDMA Description**

The compound to be used in this protocol is MDMA. This ring-substituted phenylisopropylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor [68-70]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower.

The study will employ three different dosage levels, with the lowest dosage considered active placebo and the highest dosage level considered a full experimental dose. All participants will receive an initial dose, and participants may upon agreement of the investigators, receive a supplemental dose half the size of the initial dose administered 1.5 to 2.5 hours after the initial dose.

Drug Doses for proposed study

	<b>Initial Dose</b>	<b>Supplemental Dose</b>	<b>Cumulative Dose</b>
<i>Active Placebo</i>	30 mg	15 mg	37.5 mg
	75 mg	37.5 mg	112.5 mg
<i>Full Dose</i>	125 mg	62.5	187.5 mg

### 4.3 MDMA Compounding, Doses and Labeling

This protocol will follow a randomized, double-blind design that will compare three doses of MDMA. The doses are 30 mg for active placebo, a medium-dose of 75mg, and a full dose of 125 mg. Eight participants will receive an initial dose of 125 mg of MDMA followed by an optional supplemental dose of 62.5 mg. Four participants will receive an initial dose of 75 mg MDMA followed by an optional supplemental dose of 37.5 mg, and four participants will receive an initial dose of 30 mg followed by an optional supplemental dose of 15 mg.

MDMA in bulk will be sent by [REDACTED] or his representatives at Purdue University, West Lafayette IN, to the Principal Investigator, who will take it to the pharmacist for compounding. The pharmacist will provide bulk lactose for compounding placebo and MDMA capsules. MDMA will be weighed into doses of 125, 75, 62.5, 37.5, 30 and 15 mg (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules with lactose by a pharmacist under the direct observation of the Principal Investigator who has been issued the Schedule 1 license, Capsules for initial dose will be a different color from capsules used for the supplemental dose. Lactose, in doses of equivalent dry weight, will be placed into gelatin capsules of identical appearance to those used for initial and supplemental dose MDMA by a pharmacist under the direct observation of the Principal Investigator who has been issued the Schedule 1 license. All capsules will be compounded so that they weigh the same amount, but contain varying amounts of MDMA and lactose.

All doses of MDMA will be stored in separate bottles labeled with the protocol number, drug name, lot number, unique bottle number, sponsor name and a statement that the drug is for clinical-trial-use only. Labels for each dose and bottle of MDMA will be provided by the sponsor and applied by the pharmacist. The bottle labels will be hidden from the investigator to assure blinding.

Examples of Blinded Labels

Box Label
MAPS Study# <u>XXXX</u>
Investigational Product: MDMA
Dose: Blinded (xxmg, xxmg OR xxmg, xxmg OR xxmg, xxmg)
Randomization # <u>XXX</u>
Subject Number _____
Lot #: XXXXX
Administer as per protocol
Caution-Limited by Law to Investigational Use Only

Container label MAPS Study # XXX Experimental Session #1 Dose 1 Randomization # XXX Subject # _____ Administer as per protocol Investigational Use Only	Container label MAPS Study # XXX Experimental Session #1 Dose 2 Randomization # XXX Subject # _____ Administer as per protocol Investigational Use Only	Container label MAPS Study # XXX Experimental Session #2 Dose 1 Randomization # XXX Subject # _____ Administer as per protocol Investigational Use Only	Container label MAPS Study # XXX Experimental Session #2 Dose 2 Randomization # XXX Subject # _____ Administer as per protocol Investigational Use Only
Container label MAPS Study # XXX Experimental Session #3 Dose 1 Randomization # XXX Subject # _____ Administer as per protocol Investigational Use Only	Container label MAPS Study # XXX Experimental Session #3 Dose 2 Randomization # XXX Subject # _____ Administer as per protocol Investigational Use Only		

**4.4 MDMA Accountability**

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

**4.5 MDMA Storage and Handling**

MDMA is a Schedule 1 compound and will be stored and handled in compliance with relevant Federal and State regulations. In accordance with Drug Enforcement Administration (DEA) requirements, the Principal 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 Principal Investigator with the Schedule 1 license will have 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 nurse is 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. MDMA will be administered orally with a glass of water. All doses administered will be recorded on the appropriate accountability logs.

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

records and will be maintained in a locked cabinet mounted to the wall in a locked office with an alarm system.

#### **4.6 MDMA Stability**

Complete details on the chemistry, manufacturing and control of the MDMA Hydrochloride (HCl) to be used are described in Drug Master file (DMF) # 6293. As described in that file, MDMA was prepared for human consumption in 1985 by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University. 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 US 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 from Nichols was used in an investigation of MDMA-assisted psychotherapy that took place in the US as late as 2008, and it was also used in non-sponsor supported study in 2006[71].

#### **5.0 Protocol Design**

This randomized, double-blind study will examine the safety and efficacy of MDMA-assisted psychotherapy with 30, 75 or 125 mg MDMA in sixteen veterans, ideally but not necessarily eight men and eight women, diagnosed with PTSD arising from their service in the US armed forces. Supplemental doses of half the initial dose may be administered between 1.5 and 2.5 hours after the initial dose was administered.

Prior to undergoing the first MDMA-assisted (experimental) session, all participants will undergo three 90-minute preparatory (introductory) non-drug psychotherapy sessions with a male and female co-therapist team. Participants will undergo three day-long psychotherapy sessions after receiving an initial dose of 30, 75 or 125 mg MDMA, with each experimental session scheduled three to five weeks apart. All psychotherapy sessions will be recorded to audio and video.

The same team of investigators will perform all MDMA-assisted psychotherapy sessions in their office. Participants will remain at the study site overnight accompanied by a same-sex attendant. Participants will undergo three integrative psychotherapy sessions after each experimental session, with the first integrative session occurring on the day after the experimental session.

The blinded independent rater, who will not be present during any psychotherapy sessions, will assess participant PTSD symptoms with CAPS, symptoms of depression with BDI, post traumatic growth with PTGI-C and quality of life with GAF at baseline, one month after the second experimental session and two months after the third experimental session.

When each subject completes the follow-up evaluation after the third experimental session the blind will be broken for that subject. Participants who had been assigned to receive active placebo or medium-dose MDMA will subsequently have the opportunity to enroll in the open-label study segment, or “Stage 2.” The open-label study segment will follow a nearly identical sequence of events and procedures, except that there will be a single preparatory session, and all MDMA-assisted psychotherapy sessions will be open-label with an initial dose of 125 mg MDMA followed by an optional supplemental dose of 62.5 mg.

The study will conclude with a one-year follow-up occurring 12 months after the final experimental session in Stage 1 for participants who received the full-dose condition or who did not enroll in Stage 2 after receiving either the medium or active-placebo doses in Stage 1. There will be a preliminary examination of data prior to the 12-month follow-up. Subjects who enrolled in Stage 2 will have their final follow-up 12 months after the final open-label experimental session. At the 12-month follow-up, the independent rater will assess PTSD symptoms, symptoms of depression post-traumatic growth and quality of life (via the GAF), and participants will complete a questionnaire concerning self-reported long-term effects of study participation.

There will be preliminary examination of the data before all participants have completed the 12-month follow-up.

### **5.1 Planned Duration of Protocol**

The randomized, double-blind, dose response controlled study segment (Stage 1) will last approximately four and a half months from screening and baseline evaluation up until the evaluation two months after the third experimental session. The open-label study segment for participants initially assigned to receive active placebo or medium-dose MDMA (Stage 2) will last an additional four months from the single introductory and review psychotherapy session until the evaluation two months after the final open-label MDMA-assisted psychotherapy session, for a total of about 8 months. The 12-month follow-up will occur a year after the third experimental session for all participants who complete Stage 1 only, and a year after the third open-label session for any participants who enroll in and complete Stage 2. If the investigators enroll one participant every month, the entire study will be completed in less than 3 years, with Stage 1 and Stage 2 taking less than two years and the 12-month follow-up taking an additional year.

### **5.2 Randomization and Subject Numbering**

This is a randomized, double-blind, dose comparison study with an open-label cross-over segment. Within 24 hours of the first experimental session, each participant will be assigned to one of the three dose conditions; 30 mg (active placebo), 75 mg (medium-dose) or 125 mg (full dose). Eight participants will be assigned to the full-dose condition, four participants to the 75 mg condition and four participants to the 30 mg active placebo dose condition. The study will employ a blinded randomization procedure that will

maintain the 50/25/25% ratio while maintaining the blind and ensuring that each subsequent condition assignment is not predicated on the previous assignment. A randomization monitor will generate and maintain a list of random numbers between one and 100. A randomization list program or procedure will be run to assign participants to full, medium or active placebo dose MDMA to twenty containers randomly assigned a number between 1 and 100. Prescription bottles will be randomly assigned a number between 1 and 100. The randomization monitor will also create replacement doses that retain the same ratio of experimental dose to active placebo dose condition. The randomization monitor will supervise the procedure of filling bottles with MDMA and lactose. Twenty

The investigators will contact the randomization monitor after enrolling a participant. The randomization monitor will provide the investigators with the bottle number to be used for the participant. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, the blind may be broken for an individual participant. In all other cases, the blind will be maintained up through the assessment occurring eight weeks after the third experimental session. The participant, independent rater and both investigators conducting psychotherapy will be blind to condition assignment. Participants who drop out of the study or are withdrawn by the Principal Investigator prior to the two-month follow-up will be replaced until 16 participants have completed the study.

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "001". Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 4-digit subject number. The first two digits identify the study number (08). The next two digits identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first subject enrolled in study number 08 will be 0801, second 0802, etc.

### **5.3 Recruitment and Subject Population**

Candidates for participation will be sixteen veterans with PTSD arising from their service in the US armed forces. Of the 16 subjects to be enrolled in this study, at least 12 must have PTSD of less than 10 years duration (from Iraq and Afghanistan Wars) while up to 4 may have PTSD of more than 10 years (including the Vietnam War). A subject would not be excluded for having more than one traumatic event, but would be excluded if a traumatic event not related to military service were the major contributor to the PTSD symptoms. Participants must be at least 18 years old with a diagnosis of PTSD and a screening CAPS score equal to or greater than 50 at baseline evaluation. Ideally, subjects will include eight men and eight women. Subjects of each sex who qualify and agree to participate will be accepted into the study in chronological order until eight subjects of either sex have been enrolled. Enrollment will then be limited to members of the opposite sex until eight male and eight female subjects have been enrolled. If, however, attempts to recruit equal numbers of male and female subjects turns out to result undue delay in proceeding with the study, the investigators may, after discussion with the



sponsor, revert to enrolling subjects of either sex in order to reach the goal of 16 participants.

Participants will be recruited via letters of referral sent to psychiatrists and psychotherapists, contact with veterans' organizations, advertisements or announcements placed on appropriate internet sites and the sponsor site, and word of mouth. Candidates may also be individuals who had previously contacted the investigators expressing interest in taking part in the initial study of MDMA-assisted psychotherapy for PTSD after this study had closed enrollment.

One of the investigators or their assistant will interview prospective participants by telephone to learn if they meet basic eligibility criteria. If the prospective participant is interested in taking part in the study, the investigators will provide her or him with consent materials for review and consideration through postal mail or direction to a website. If, after review, an applicant remains interested in taking part in the study, then he or she will meet with the investigators to complete the consent process. Applicants will complete a quiz to assess their understanding of the consent forms. Investigators will then review the quiz responses with the prospective participant to ensure that he or she correctly understands study procedures, risks and benefits.

### **5.3.1 Inclusion Criteria**

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

1. Meet DSM IV criteria for current PTSD with a duration of 6 months or longer resulting from traumatic experience during military service.
2. have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
3. are at least 18 years old;
4. If in ongoing psychotherapy at the time they are recruited into the study, participants may continue to see their outside therapist during the course of the study. They must sign a release for the investigators to communicate directly with their therapist. They may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session 2 months after the third experimental session. Subjects who do not live within reasonable driving distance of the study site must have a therapist in the area in which they live whom they can call on for support and evaluation if necessary.
5. are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician.
6. agree that, for one week preceding the MDMA session will refrain from:
  - a. taking any herbal supplement (except with prior approval of the research team);

- b. taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team);
  - c. taking any prescription medications, with the exception of birth control pills, thyroid hormones or other medications approved by the research team);
7. agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before the experimental session;
8. refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA session;
9. agree not to use caffeine or nicotine for 2 hours before and 6 hours after the dose of MDMA;
10. are willing to remain overnight at the study site;
11. 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;
12. are willing to be contacted via telephone for all necessary telephone contacts;
13. are of childbearing potential who have a negative pregnancy test and agree to use an effective form of birth control;
14. are proficient in speaking and reading English;
15. agree to have all clinic visit sessions recorded to audio and video.

### **5.3.2 Exclusion Criteria**

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

1. are pregnant or nursing, or are women of child bearing potential who are not practicing an effective means of birth control;
2. have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 or, dissociative identity disorder
3. have evidence or history of coronary artery disease or cerebral or peripheral vascular disease, hepatic disease with abnormal liver enzymes, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration;
4. have hypertension using the standard criteria of the American Heart Association (values of 140/90 or higher assessed on three separate occasions [72]) , unless their hypertension has been successfully treated and is currently well-controlled on antihypertensive medicines, In this case subjects with well-controlled hypertension may be enrolled if they pass additional screening to rule out underlying cardiovascular disease (see methods).
5. have liver disease with the exception of asymptomatic subjects with Hepatitis C who have undergone additional evaluation (see methods). Subjects with Hepatitis C may be enrolled if they have received appropriate screening (see methods.)
6. have history of hyponatremia or hyperthermia;

7. weigh less than 48 kg;
8. would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
9. have used “ecstasy” (material represented as containing MDMA) more than five times or at least once within 6 months of the MDMA session;
10. require ongoing concomitant therapy with a psychotropic drug;
11. meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days;
12. are not able to give adequate informed consent;
13. have any current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol.

## 6.0 Methods

After consenting to take part in the protocol, participants will be screened by a physician who will obtain medical and psychological history by interview and perform a general physical examination, brief neurological exam and clinical laboratory assessments.

### *Additional screening for specific conditions:*

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 completion of any recommended treatment, if the Hepatitis C is judged by this physician to be relatively stable and of mild severity the person may be enrolled if there are no other contraindications.

If the potential subject has well-controlled hypertension and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam or ECG, and if the Principal 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 cardiovascular disease the person may be enrolled if there are no other contraindications.

Participants will also undergo the Structured Clinical Interview for Diagnoses (SCID) and assessment via CAPS for psychiatric diagnosis and to determine participant eligibility. If, after reviewing all information, the investigators conclude that a participant is eligible they will arrange and schedule at least one introductory session with the investigators.

After undergoing three 90-minute non-drug introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions scheduled three to five weeks apart, during which they will randomly receive either the active placebo, medium-dose or full-dose MDMA on all three occasions. Participants will undergo one non-drug-psychotherapy session the day after each experimental session and at least two additional 90 minute non-drug integrative psychotherapy sessions between experimental sessions. For subjects who live within easy driving distance of the study site, these integrative psychotherapy sessions will be scheduled approximately a week apart. For subjects living farther away, these sessions may be scheduled at less regular intervals to accommodate travel logistics (for example, two may occur in the week following the preceding experimental session and the other might occur a day or two prior to the subsequent experimental session).

PTSD symptoms will be assessed by an independent rater who will be blind to condition assignment and will not be present during any of the psychotherapy sessions. Subjects will be instructed not to reveal to the independent rater their own opinion about which dose of MDMA they received. The rater will assess PTSD symptoms and quality of life measures of symptoms of depression and post-traumatic growth prior to MDMA-assisted psychotherapy at baseline, one month after the second experimental session and two months after the third experimental session. All psychotherapy sessions, including MDMA-assisted experimental sessions, will be recorded to audio and video, with all recordings preserved for research purposes. Participants may receive any session recordings upon request.

As safety measures, vital signs and a measurement of psychological distress will be assessed during the MDMA sessions. Level of psychological distress will be measured with the 7 point Subjective Units of Distress (SUD) scale immediately before MDMA administration and approximately every 90 minutes thereafter for the duration of the MDMA sessions. Suicidality will be assessed throughout the course of the study with the clinician-administered C-SSRS. The C-SSRS will be administered during nearly every visit involving face to face contact with the investigators conducting psychotherapy, and on two of six days of telephone contact.

## **6.1 Assessments and Measures**

The following outcome and safety measures will be employed in Stage 1 and Stage 2, following a nearly identical sequence of events, except that participants in Stage 2 will have one and not three preparatory (introductory) sessions.

### **6.1.1 Outcome Measures**

The primary outcome measure will be the Clinician Administered PTSD Scale (CAPS), a clinician-scored measure for PTSD diagnosis and measure of symptom intensity and severity. The CAPS provides a means to evaluate the frequency and intensity dimensions

of each symptom, impact of symptoms on the patient'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 takes approximately one hour to complete. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [73, 74]. An independent rater will assess all participants at study baseline, one month after the second experimental session and two months after the third experimental session. The same independent rater will assess all participants enrolled in stage 2 at the same times.

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, with scores ranging from 0 to 100, with 100 reflecting superior function and zero reflecting serious risk of causing harm to the self or others. The GAF will be recorded by the independent rater at baseline, one month after the second MDMA session and two months after the third and final MDMA session in both Stage 1 and Stage 2.

The Beck Depression Inventory (BDI) is a 21-item self-report measure of depressive symptoms [75, 76] that will serve as a measure of depression. It takes five to ten minutes to complete. Participants will complete the BDI at the same times when the CAPS is administered.

The Post Traumatic Growth Inventory-Current (PTGI-C) is an adaptation of the Post Traumatic Growth Inventory assessing perceived benefits or growth in the two weeks preceding administration, using the same items from the original measure but adapting language to reflect recent experiences [77, 78]. It is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; (relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life. Participants will complete the PTGI-C at the same points in time when they complete the CAPS and BDI.

### **6.1.2 Safety Measures**

Participants will rate their current degree of subjective distress with a single-item, self-report scale, the SUD scale, repeatedly during the MDMA session, with the degree of distress marked along seven points. Subjective psychological distress will be measured periodically throughout each experimental session,

Blood pressure, heart rate (as pulse) and temperature will be assessed periodically during each experimental session. Blood pressure and pulse will be measured at the outset of the experimental session, once every 15 minutes for the first four hours of the MDMA-assisted session and every 30 minutes for another two hours. Participants with controlled hypertension will have blood pressure and pulse assessed every 15 minutes for the first five hours and every thirty minutes for the next three hours. More frequent measures will be taken as per the judgment of the Principal Investigator if the established thresholds of

160 systolic, 110 diastolic or pulse 110 are exceeded. Blood pressure and pulse will be assessed via an automatically inflating cuff. Body temperature will be assessed via tympanic thermometer every 60-90 minutes.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [79]. It consists of a "Baseline" form that assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation, and intensity. The C-SSRS consists of a series of questions, and can be administered during face-to-face interview or over the telephone. The C-SSRS will be administered 24 times during the randomized study; at baseline, after the second preparatory session, twice during each experimental session (once just prior to drug administration and once five to six hours after drug administration), after each integrative session, on the first and last days of daily telephone contact occurring after an experimental session, and on the visit which takes place approximately two months after the third experimental session. Participants undergoing medication washout will complete the C-SSRS once prior to and once after medication washout, using the times above if possible but with additional measures used if none of the scheduled times occur just prior to or after medication washout.

Spontaneously reported side effects, Adverse Events (AEs) and SAEs will be recorded during all three experimental sessions and for a period of seven days after each experimental session for a total of 27 times. The investigators will also assess general well-being during each introductory session, at each integrative session and during telephone calls for seven days following integrative sessions that occur a day after an experimental session.

The Reactions to Research Participation Questionnaire (RRPQ) is intended to 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, and is not an outcome measure [80]. It is administered once at the conclusion of the subject's final follow-up before the long-term follow-up, after either Stage 1 or Stage 2.