

PROTOCOL MP-8

IND #63,384

December 17, 2009
Amendment 1: March 3, 2010 Version 2

**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)**

SPONSOR Multidisciplinary Association for Psychedelic
Studies (MAPS)
309 Cedar Street, #2323
Santa Cruz, CA 95060

SPONSOR DESIGNEE Rick Doblin, Ph.D.
[REDACTED]

PRINCIPAL INVESTIGATOR Michael C. Mithoefer, M.D.
[REDACTED]

MEDICAL MONITOR Julie Holland MD
[REDACTED]

STUDY MONITOR Berra Yazar-Klosinski PhD
[REDACTED]

For trial related emergencies: Phone number [REDACTED]

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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
HCV	Hepatitis C Virus
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-methylenedioxymethamine
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 U.S. 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

	Initial Dose	Supplemental Dose	Cumulative Dose
<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 Dr. David Nichols Ph.D 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 after all participants complete experimental sessions and the two-month follow-up, but before all participants have completed the 12-month follow-up. The interim data analysis will be conducted for safety and efficacy.

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.

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 and with sealed envelopes that will permit unblinding for an individual subject if required. 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 by opening the appropriate envelope, which will be kept sealed in a locked safe in the investigator's office at the study site so it would be easily available in case of emergency. 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 (equal to or less than an estimated two hours' drive from 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. must provide a contact (relative, spouse, close friend or other caregiver) who is willing and able to be reached by the investigators in the event of a participant becoming suicidal;
 15. are proficient in speaking and reading English;
 16. 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, as determined through psychiatric interview, responses to CSSRS and through the clinical judgment of the investigator, or who, in the judgment of the investigator, are likely to require hospitalization during the course of the study;
 9. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist;
 10. have used “ecstasy” (material represented as containing MDMA) more than five times or at least once within 6 months of the MDMA session;
 11. require ongoing concomitant therapy with a psychotropic drug;
 12. 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;
 13. are not able to give adequate informed consent;
 14. 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 after completion of any recommended treatment, if the Hepatitis C is judged by this physician to be relatively stable and of mild severity the person may be enrolled if there are no other contraindications.

If the potential 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 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.

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 (equal to or less than an estimated two hours drive time of the 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 time, and all participants will be assessed at 12 month follow-up.

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, and at 12-month follow up.

The Beck Depression Inventory (BDI) is a 21-item a 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 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. Serious adverse events (SAEs), adverse events of concern to the subject and any adverse events requiring medical intervention will be collected throughout the protocol. 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.

Time & Events MP8 Stage 1	Screen/Baseline		Preparatory	Experimental Session 1		Experimental Session 2			Experimental Session 3		Follow-Up
Visit #	Pre-Study	V1	V 2,3,4	V5	V 6,7,8	V9	V 10,11,12	V13	V14	V 15,16,17	V18
Type of Visit	Screening may take place over more than one day	Baseline	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Outcome	Experimental Session 3	Integrative Sessions	Follow-Up & Outcome
Visit Timing or Study day or Window	Up to 1 month prior to Visit 1	Day 1	Approx 1 week apart	3-5 weeks post baseline	Approx. 1 week apart ^A	3-5 weeks post V5	Approx. 1 week apart ^A	1 month post V9	3-5 weeks post V9	Approx. 1 week apart ^A	May happen over more than 1 day. 2 months post V14
Initial Phone Screen	X										
Informed Consent	X										
Medical/Psychiatric History	X										
General Physical Exam (BP, Pulse, Temp, brief systems check)	X										
Brief Neurological Exam	X										
ECG	X										
SCID	X										
Clinical LabTests, w/ HIV, HCV test	X										
Collect Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Medication Taper (if applicable)	X	X									
Study Enrollment after meeting I/E		X									
Record to Audio/Video			X	X	X	X	X		X	X	
General Well-Being		X	X	X	X	X	X		X	X	X
Drug Screen	X			X		X			X		
Pregnancy Screen (if applicable)	X			X		X			X		
Complete Randomization Procedure				X ^C							
CAPS, GAF, BDI and PTGI-C With Independent Rater	X		X ^B					X			X
C-SSRS		X	X ^H	X ^{D, E, F}	X	X ^{D, E, F}	X	X	X ^{D, E, F}	X	X
Administer IP Drug+Therapy				X		X			X		
Monitoring of BP, Pulse and Temp.				X		X			X		
SUDS				X ^{E, G}		X ^{E, G}			X ^{E, G}		
Beliefs of Condition Assignment					X ^L		X ^L			X ^L	
Overnight Stay				X		X			X		
Integrative Therapy Session					X		X			X	
RRPQ											X ^I
7 days Integrative Telephone Contact					X ^J		X ^J			X ^J	
Adverse Events Requiring Dr. Visit				X	X	X	X	X	X	X	X
Spontaneously Reported Side Effects				X	X	X	X		X	X	
Adverse Events of Concern		X	X	X	X	X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X	X	X	X	X
Unblinding ^K											X

^A=First Integrative session is 1 day after exp session ^B=repeat before V5 ONLY if meds are tapered ^C= Within 24 hrs prior to 1st exp. session ^D=Approximately 6 hours post MDMA ^E=at the beginning of the session ^F=as needed ^G=Approximately every 60 minutes ^H=Given on 2nd preparatory session only (V3) ^I= Only for subjects starting Long term Follow up and not going to Stage 2 ^J=For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days ^K=Subjects will go onto 1 Year Long Term Follow up or Stage 2 Stage L= On the day of the 1st integrative session following the Exp. Session

Time & Events MP8 Stage 2	Preparatory	Experimental Session 1		Experimental Session 2			Experimental Session 3		Follow-Up	Long Term Follow-Up
	Visit #	V19*	V20	V 21,22,23	V24	V 25,26,27	V28	V29	V 30,31,32	
Type of Visit	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Outcome	Experimental Session 3	Integrative Sessions	Follow-Up & Outcome	Follow-Up & Outcome
Visit Timing or Study day or Window	Within 1 month of V18*	1 week post V19	Approx. 1 week apart ^A	3-5 weeks post V20	Approx. 1 week apart ^A		3-5 weeks post V24	Approx. 1 week apart ^A	May happen over more than 1 day. 2 months post V29	May happen over more than 1 day. One Year After V14 or V29
Confirm Informed Consent	X									
Confirm Inclusion/Exclusion	X									
Enrollment in Stage 2	X									
Collect Concomitant Medication	X	X	X	X	X	X	X	X	X	
Record to Audio/Video	X	X	X	X	X		X	X		
General Well-Being	X	X	X	X	X		X	X	X	
Drug Screen		X		X			X			
Pregnancy Screen (if applicable)		X		X			X			
CAPS, GAF, BDI and PTGI-C With Independent Rater	Use V18*					X			X	X
C-SSRS	X ^H	X ^{D, E, F}	X	X ^{D, E, F}	X	X	X ^{D, E, F}	X	X	X
Administer IP Drug+Therapy		X		X			X			
Monitoring of BP, Pulse and Temp.		X		X			X			
SUDS		X ^{E, G}		X ^{E, G}			X ^{E, G}			
Overnight Stay		X		X			X			
Integrative Therapy Session			X		X			X		
RRPQ									X	
7 days Integrative Telephone Contact			X ^J		X ^J			X ^J		
Adverse Events Requiring Dr. Visit	X	X	X	X	X	X	X	X	X	X
Spontaneously Reported Side Effects		X	X	X ^J	X		X ^J	X		
Adverse Events of Concern	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X
Complete Stage 2 go to 1yr Follow-up									X	
LTFU Questionnaire										X
Termination Visit										X

Long Term Follow up after Stage 1 or Stage 2

* If Visit 19 is more than 1 month after V18 then the measures from V18 will need to be repeated prior to starting Stage 2

A =first session is 1 day after exp session D =Approximately 6 hours post MDMA E =at the beginning of the session F =as needed G =Approximately every 60 minutes H =Given on 2nd preparatory session only (V3) J =For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days

6.2 Visit Descriptions

6.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study, Visit 1)

After giving written informed consent each participant will be assigned a screening number. The screening number will be used on all subject records prior to enrollment. Participants will provide a medical and psychological history through interview and will undergo a general physical examination performed by a physician who is not one of the investigators. The examination will involve the following procedures: blood pressure, pulse, height, weight, body temperature, examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities, brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function) , electrocardiogram (ECG), clinical laboratory assessments to determine study eligibility (see 10.0 for list of laboratory tests). In addition, Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) serology will be performed. If there is a confirmed positive HIV serology, it will be kept confidential with the exception of reporting to the South Carolina Department of Health and Environmental Control as required by law, with the Department of Health informing the home state of any individual not residing in South Carolina. Likewise HCV serology will be kept confidential except for reporting to the South Carolina Department of Health and Environmental Control within seven days of discovery as required by law. Appropriate referral for counseling and treatment will be made if necessary. The clinical laboratory values will not be captured in the Case Report Form (CRF), but will be used to establish eligibility and will be kept with the subject's source record. A urine-dip pregnancy test for females of childbearing potential will be performed as well. If, upon examination, there are questions raised about possible medical problems, the investigators will request a review of participant medical records and request additional tests or assessments as indicated. If it is determined that the participant has Hepatitis C or well-controlled hypertension, further evaluation will be performed as described in section 6.0.

After eligibility is confirmed the participant will be considered enrolled and will be issued a subject number and contacted to schedule the introductory non-drug psychotherapy sessions and first experimental session. Any participant who must discontinue a medication will, after consultation with the prescribing physician, be given a schedule to begin tapering off that medication so washout will be completed before the first experimental session, with the interval between the start of washout and the first experimental session being at least five times the drug's half-life. The first experimental session will be scheduled to occur after washout is complete.

A blinded independent rater who will not be present during any of the therapy sessions will administer the CAPS and assess the participant on the GAF. The C-SSRS will also be administered at screening to assess suicide risk. Suicide risk will also be assessed via psychiatric interview. The principal investigator and independent rater will use medical records, communication with the participant's treating psychiatrist or therapist if applicable and psychiatric interview to assess potential risk to others. The participant will complete the BDI and PTGI-C.

The entire visit should take between 1.5 and 2.5 hours. Screening may take place over more than one day and up to one month prior to visit 1.

Participants 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).

6.2.2 Preparatory Sessions (Visits 2-4)

The investigator will inquire about any possible changes in the participant's health to ensure that they continue to meet eligibility criteria and if applicable, will confirm that they have adhered to the schedule for tapering off medications.

The participant will undergo three 90-minute preparatory non-drug psychotherapy sessions with the investigators at their offices. During these sessions the investigators will gather more detailed history, answer any questions the participant may have, and work toward forming a strong therapeutic alliance. The participant and investigators will discuss goals for the MDMA sessions. They will review the procedures and therapeutic approach, following standard procedures and techniques discussed in the sponsor-developed treatment manual. The investigators will prepare the participant for the upcoming experimental sessions and promote an atmosphere of safety in which to confront traumatic experiences and powerful emotions.

During the third and last introductory session, the investigators will supply the participant with a set of instructions and restrictions for conduct 24 hours prior to receiving MDMA, including restrictions on food and alcohol consumption. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before the MDMA session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA session. Participants must not use caffeine or nicotine for 2 hours before and 6 hours after the dose of MDMA.

Unless a participant is still undergoing medication washout, participants will complete the C-SSRS just prior to beginning the second preparatory session. Participants still undergoing medication washout will complete the C-SSRS during the third preparatory session or at a point after washout is complete.

The attendant, described below, will remain with the participant during each overnight stay after each MDMA-assisted psychotherapy session. He or she will be of the same sex as the participant, will have a healthcare background, and will undergo specific training for the role. If a participant would like another individual present during the MDMA session, a meeting between the investigators and that individual will be scheduled during the introductory session. Such an individual will not replace the night-time attendant. Introductory sessions will be recorded to audio and video, and participants can receive copies of one or more introductory sessions upon request. All SAEs will be recorded from the time the participant is enrolled at Visit 1.

6.2.3 MDMA Session (Visits 5, 9, and 14)

All participants will receive three double-blind experimental sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Each experimental session will last approximately eight hours followed by an overnight stay at the study site. Experimental sessions will be conducted by the male and female co-therapist team. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions, and all procedures except drug dose will be the same for participants assigned to the full, medium and active placebo dose conditions.

On the day of the MDMA session, the participant will arrive approximately one to one and a half hours prior to the MDMA session. Continuing eligibility will be confirmed, with confirmation of eligibility including a urine drug screening and, if appropriate, a urine pregnancy test. If the subject continues to meet criteria and the participant reports that he/she followed appropriate rules and restrictions, the session will proceed; a positive pregnancy screen is cause for withdrawal from the protocol, a positive drug screen will be reviewed by the investigator and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study. The sponsor and principal investigator will follow any pregnancy detected after the occurrence of an experimental session to outcome.

Before MDMA is administered, the therapists and participant will discuss and review the participant's goals, intentions and concerns and some of the commonly experienced effects of MDMA. Participants will complete the SUD just prior to initial dose administration.

At approximately 10:00 A.M., participants will receive the initial dose of MDMA along with a glass of water. The participant will sit or recline on comfortable furnishings, and there will be eyeshades and a program of music available if the participant wishes to use them. They 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 [81-83]. The investigators will also encourage periods of time in which the participant remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of their inner experience, in accordance with the principles of MAPS' treatment manual [84]. Water and electrolyte containing fluids will be available ad lib throughout the session within the limits described in Appendix A. Food will be available during the latter part of the session. The investigators will record the entire session to video and audio. Participants may receive a copy of audio or video recordings of at least one experimental session upon request. The participant will be encouraged to spend much of the time focusing attention on their inner experience without talking, but may speak to the investigators whenever they wish, and will receive guidance and support as needed. After the first hour, if the participant has not spoken spontaneously, the investigators will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the investigators will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging.

Suicidality will be assessed with the C-SSRS twice during each experimental session (approximately one hour before and five to six hours after drug administration),

Blood pressure and pulse will be measured at the outset of the experimental session, once every 15 minutes for the first 4 hours of the MDMA-assisted session and every 30 minutes for another 2 hours. More frequent measures will be taken as described in section 6.1.2 if the established thresholds are exceeded, or if the subject has a diagnosis of hypertension. Participant body temperature will be measured via tympanic thermometer every 60-90 minutes. Participants will complete the SUD every 90 minutes, until the session is over, allowing a window of plus/minus 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the investigators can make a greater number of SUD measurements as their clinical judgment dictates. The investigators will record any spontaneously reported side effects during the session

A supplemental dose half the size of the initial dose will be administered 1.5 to 2.5 hours after the initial dose upon mutual agreement between the investigators and participant.

Approximately six hours after drug administration, the investigators will administer the C-SSRS.

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 therapists.

The investigators will remain with the participant until the physical and psychological effects of the session have substantially subsided and the subject is judged to be in a stable condition and appears to have returned to baseline mental status. The investigators will end recording to audio and video when they have established that the participant returned to baseline function or is very close to doing so. Both of the investigators conducting psychotherapy reside near the study site and one or both can quickly return to the site if necessary. Throughout the study, at least one of the investigators, or a physician who is covering for them if they are not available, will remain available to participants via 24-hour cellular telephone.

The participant will remain at the study site overnight, in a comfortably furnished suite that allows for accompaniment by a significant other, and the attendant. The attendant will remain in the building during the overnight stay, even if a significant other is present. The attendant will attend to the subject's needs such as food and fluids during the overnight stay. The attendant will be an individual with previous training or experience in supporting individuals in psychological distress. The attendant may be anyone with some training or background in health care, particularly in psychiatric care. If there is an emergency or the participant needs additional support, the attendant can contact the investigators. The participant and if applicable, his or her significant other, will also receive contact information for the investigators during the overnight stay in the case of an emergency or request for additional support. Participants 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.

Participants will be instructed not to use caffeine or nicotine for 6 hours after the dose of MDMA. Spontaneously reported side effects, AEs of concern to the participant, and AEs requiring a doctor's visit will be collected starting on the day of the MDMA session through the seventh telephone daily telephone call. All SAEs occurring during study enrollment will be recorded.

6.2.4 Integrative Sessions 24 Hours after Experimental Session (Visits 6, 10, 15)

On the morning after the MDMA session, the participant will meet with both investigators during a 90-minute integrative psychotherapy session. Participants will complete the C-SSRS just prior to beginning each integrative session. At the beginning of this session, the participant and both investigators conducting psychotherapy will indicate their beliefs concerning participant condition assignment. The participant and investigator will then discuss and review events, thoughts, feelings and memories that occurred during the experimental session. If necessary, the investigators will help the participant to reduce any residual psychological distress he or she may be experiencing. The therapists will also encourage exploration of any new insights and perspectives resulting from states of acceptance, feelings of intimacy, and reduced fear that may have occurred during MDMA sessions and that may be applicable to emotionally distressing situations in everyday life. The investigators will be supportive, validating the MDMA experience and facilitating understanding and emotional clearing. The investigators will assess participant mental health and the presence of any remaining side effects during integrative psychotherapy sessions. Integrative psychotherapy sessions can also serve as an opportunity for the investigators to gather information in an unstructured manner about the effects of MDMA on the participant.

After this psychotherapy session, a person previously selected by the subject will provide a ride home. If the participant is unable to locate an individual to take him or her home, the investigators will arrange an alternative means of transportation. The entire integrative psychotherapy session will be recorded to audio and video. Participants may receive copies of this session upon request. Therapists will be accessible if the participant needs support outside the scheduled integration sessions.

Spontaneously reported side effects, AEs of concern to the participant, AEs requiring a doctor's visit and concomitant medications for treatment of AEs will be collected. All SAEs will be recorded.

6.2.5 Daily Telephone Contact for Seven days after an Experimental Session

Starting on the day of the non-drug integrative psychotherapy session following each experimental session, one of the investigators will contact the participant via telephone daily for one week. The telephone contact will be for a brief check-in lasting 5 to 15 minutes, or as long as necessary to address any participant's concerns or difficulties integrating their experience and to assess participant well-being. Additional telephone

contact can be initiated at the request of the investigators or participant. Spontaneously-reported side effects, AEs of concern to the participant, AEs requiring a doctor's visit and concomitant medications for treatment of AEs will be collected. All SAEs will be recorded. On the second and seventh day of telephone contact, the C-SSRS will be administered to monitor for suicide risk.

If the investigators are unable to reach a subject by telephone despite repeated attempts, every effort will be made to contact their outside physician or a family member to be sure they receive any support they need. If the investigators eventually contact the person, this participant would be permitted to remain enrolled in the study only if measures could be put in place to assure that such a problem would not recur.

6.2.6 Integrative Psychotherapy Between Experimental Sessions

The participant will have 60 to 90-minute scheduled non-drug psychotherapy sessions with both psychotherapist investigators during the interval between the first and second experimental session, between the second and third experimental sessions and after the third experimental session (See Time and Events Table). The investigators may conduct more sessions if they and the participant deem it necessary. The purpose of these sessions is to provide continued support for the participant as she or he considers his or her experiences during the experimental sessions and strives to integrate them into their lives. The investigators will use clinical judgment to assess the participant's psychological well-being during this period of time. Suicidality will be assessed with the C-SSRS. Each integrative session will be recorded to audio and video, and participants may receive a copy of one or more integrative sessions upon request. If there are any indications of continuing anxiety or distress, the investigators may arrange to address it in a specially scheduled non-drug therapy session, through continuing telephone contact, or at the next regularly scheduled non-drug therapy session. The participant may also initiate contact with the investigators at any time throughout the study.

AEs of concern to the participant, and AEs requiring a doctor's visit will be collected starting on the day of the MDMA session through the seventh telephone daily telephone call. If an integrative session falls within the seven-day period of telephone contact, it will replace the day of telephone contact, and spontaneously reported side effects will be recorded as reported during the session. Any spontaneously reported effects occurring outside of this period will be recorded as AEs. All SAEs will be recorded.

Evaluation One Month After the Second Experimental Session (Visit 13)

Participants will meet with the independent rater for a 90 to 120-minute evaluation one month after the second experimental session and prior to the third experimental session. The independent rater will administer the CAPS, BDI, PTGI-C, and assess participant quality of life with the GAF. Suicidality will be assessed with the C-SSRS. All SAEs will be recorded.

6.2.7 Evaluation Two Months after the Third Experimental Session

The final evaluation in the double-blind portion of the study will occur two months after the third experimental session. Participants will meet the independent rater for 90 to 120

minutes. The independent rater will administer the CAPS, BDI, PTGI-C and C-SSRS, and the independent rater will assess the participant on the GAF. The measures are described earlier in "Assessments and Measures." All SAEs will be recorded.

6.2.8 Unblinding and Opportunity for Participants in Active Placebo and Medium Dosage Condition to Enroll in Open-Label Study Segment ("Stage 2")

After completing all assessments and measures at the evaluation two months after the third experimental session, the participant will meet with the investigators for approximately one hour, and the blind will be broken for that individual. Participants assigned to the full-dose condition and participants assigned to the other conditions who decline enrolling in Stage 2 will complete the Responses to Research Participation Questionnaire. Participants who are not enrolled in Stage 2 may return to taking psychiatric medications. The independent rater will remain blind to condition assignment at this time.

After unblinding, the investigators will ask all participants assigned to active placebo or medium dose MDMA if they wish to enroll in Stage 2. Participants who elect to enroll in Stage 2 will undergo a course of therapy and evaluation nearly identical to the randomized study, but with full-dose MDMA given in an open-label context. The investigators will consider participants who have completed all Stage 1 study visits and who do not wish to enroll in Stage 2 as having completed the study. These individuals will complete the RRPQ.

6.2.9 Open-Label Study Segment for Active Placebo and Medium Dosage Participants ("Stage 2")

Participants assigned to receive active placebo or medium-dose MDMA during the randomized study segment will undergo three open-label MDMA-assisted psychotherapy sessions that follow a course and schedule similar to the randomized study except that participants undergo one instead of three introductory sessions. After giving written informed consent, participants enrolled in Stage 2 will meet with both investigators conducting psychotherapy for a single review and re-introductory psychotherapy session before the first open-label MDMA-assisted psychotherapy session. Spontaneously reported side effects, AEs and SAEs will be collected and reported in the same manner as during the randomized study segment.

6.2.10 Assessment Two Months after Third Open-Label Session

All participants in Stage 2 will be assessed by the independent rater two months after their final open-label session. At that visit, the independent rater will administer the CAPS, and complete the GAF, and participants will complete the BDI, PTGI-C, the C-SSRS and the RRPQ. From this point forward subjects will no longer be required to refrain from taking psychotropic medications. All SAEs will be recorded.

6.2.11 Evaluation 12 Months After Final Experimental Or Open Label Session

All participants who completed Stage 1 only will be evaluated 12 months after their third experimental session, and all participants who completed Stage 2 will be evaluated 12 months after their third open-label MDMA-assisted psychotherapy session. The

independent rater will administer the CAPS and complete the GAF, PTGI and BDI. Suicidality will be assessed with the C-SSRS. Participants will also complete a questionnaire assessing positive and negative long-term effects of the study. Outcome measures will either be completed over the telephone or at the study site, and the participant will return self-report questionnaires in envelopes supplied by the investigators with the study site listed both as the mailing and return address.

6.3 Removal of Participants from the Study

Participants can withdraw consent at any time without prejudice. The investigator can withdraw a participant if, in his or her clinical judgment, it is in the best interest of the participant or if the participant cannot comply with elements of the protocol that are critical for safety or necessary for the scientific integrity of the study. If the investigator withdraws a participant from the study, the investigators will explain the reason for withdrawing the participant.

Participants who withdraw will be clinically monitored after withdrawal, the cause of which will be recorded in the participant's source records and CRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE resolutions, if applicable.

6.4 Premature Discontinuation of the Study

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform the study subjects and will arrange appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor, will be treated in accordance with federal and local regulations. Participants will still receive recordings of sessions if they request them.

7.0 Risks Of Study Participation

7.1 Screening

Medical data will be collected via history and physical examination and measurement of vital signs, laboratory tests, and ECG. If indicated, additional procedures such as exercise tests and ultrasound imaging will be administered. Submitting to a full medical examination may be time consuming, and may be distressing or uncomfortable for some. Because medical examinations are part of the screening procedure, they cannot be omitted from the study design.

Psychological assessments will be obtained through interviews. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of PTSD symptoms are used during screening, they cannot be avoided. The investigators have experience working with people with PTSD, and they will seek to reduce anxiety and distress during these interviews.

7.2 Risks and Discomforts Associated with Drawing Blood

Prior to enrollment, blood will be drawn as part of screening to assessing eligibility. Temporary discomfort may arise as a result of sampling blood. Participants may experience temporary discomfort at the blood-draw site. There is also a remote possibility of inflammation or infection at the blood-draw site.

7.3 Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy

During non-drug and MDMA-assisted psychotherapy sessions, participants 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 and experimental sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention (MDMA-assisted psychotherapy), 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.

Participants may discuss emotionally distressing or embarrassing issues during their MDMA session. This may cause psychological distress.

All psychotherapy sessions will be recorded to audio and video and participants may have access to recordings if they request them. Participants may feel uncomfortable with having their sessions recorded. The recordings will be used for developing a manualized form of MDMA-assisted psychotherapy to be used in future research, and participants may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment. Participants 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 investigators, trainees or regulatory agencies.

7.4 Risks of Receiving MDMA

Side effects of MDMA are modest and have generally not been associated with serious discomfort by volunteers in previous studies in non-psychiatric populations. Common side effects include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common side effects include restlessness, parasthesias (odd somatic feelings, such as tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, and nystagmus (eye-wiggling). These effects are transient and wane as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects are reported less often than acute effects. More information on drug side-effects is contained in the Investigator's Brochure (IB).

MDMA may produce mild alterations in sensory perception and altered perception of time [40, 59, 67]. Women may be more sensitive to these effects than men [61]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change [46].

7.4.1 Cardiovascular 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. Participants enrolled in controlled trials with MDMA (approximately 5% per trial) have had elevations in blood pressure above 200/100 mmHg or above a cut-off of 140/90 mmHg [67, 85]. Table 2 shows the degree of increase in vital-sign measurements in the investigators' recently completed clinical trial. No subjects in the completed trial or other clinical trials using MDMA have required any clinical interventions for elevated blood pressure, pulse or temperature, and all values returned to normal spontaneously. While maximum peak blood pressure during a given session in some cases rose above the cut-off for making more frequent measures (160 Systolic Blood Pressure (SBP) or 110 Diastolic Blood Pressure (DBP)). The degree of additional blood pressure and pulse elevation after a second dose of MDMA that is half the original dose and given 1.5 to 2.5 hours after the first dose is minimal. Preliminary data gathered by Dr. Michael Mithoefer, the Principal Investigator who recently conducted a study of MDMA-assisted psychotherapy in 21 participants with PTSD, demonstrates that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose.

Table 2. Physiologic Data: Increases over Baseline and Range of Values

All Experimental Sessions

Highest recorded increase over baseline per experimental session	MDMA	Placebo
	Mean increase (St. Dev.) [Range of values]	Mean increase (St. Dev.) [Range of values]
Systolic blood pressure, mmHg	28.21 (14.11) [96-179]	13.38 (10.40) [83-157]
Diastolic blood pressure, mmHg	15.38 (6.85) [56-113]	10.94 (6.93) [60-102]
Heart rate, beats/minute	28.13 (11.87) [60-141]	16.69 (12.35) [68-107]
Temperature, °C	0.72 (0.52) [36.6-37.83]	0.42 (0.32) [36.39-37.76]

Group comparisons of vital signs were tested for change pre-session (15 minutes prior) to highest recorded and pre-session to post-session (6 hours post) using *t*-tests. There was a significantly greater increase in all physiologic measures from pre-session to highest recorded value during experimental sessions for the MDMA group than for the placebo group ($p < .05$). There were no significant differences when comparing changes from pre-session to post session ($p > .05$). All values returned to pre-session norms by six hours after session completion.

7.4.2 Psychological Distress

Psychological distress from MDMA could arise at any time from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following an MDMA session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from the investigator, with occasional use of benzodiazepines for anxiety. In the proposed study, participants will have volunteered for the sessions with the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, anxiety, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. Investigator responses to psychological distress are discussed in detail in Appendix A.

Less commonly, mild anxiety and depressed mood are reported 1–3 days after MDMA administration [60, 61, and see the IB]. At least some of the physiological or psychological side effects listed above are very likely to occur. Proper preparation and follow-up support will reduce the impact of acute or sub-acute side effects, so that participants are not likely to be unduly troubled by them.

7.4.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body Temperature [61], and ambient temperature does not enhance or attenuate this slight elevation in humans. Maximum body temperature could rise above normal temperature, as with the maximum peak of 100° Fahrenheit (F), or 37.7 Celsius (C) during the first experimental session in the sponsor's recent Phase 2 trial (n = 23, MDMA and placebo conditions combined), but body temperature returned to normal without treatment other than simply lowering the ambient temperature, which may or may not have been necessary.

7.4.4 Immunological Changes

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. A research team in Spain has studied the acute immunological effects of one or two doses of 100 mg MDMA [86-88]. Findings included a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings [89-91]. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [88, 92]. 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. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose [93, 94], and a second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose [94]. Given this data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose will slightly enhance the immunological effects set in motion by the first dose. Previous Phase 1 studies have not reported any indication of increased risk of illness occurring after MDMA administration.

7.4.5 Abuse Liability

MDMA was classified as a Schedule 1 compound in 1985, largely on the basis of its growing popularity at nightclubs and parties in the early to mid-1980s. The DEA placed MDMA in Schedule 1, a category defined to include drugs with high abuse potential and no known medical use [95]. Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA [96-98]. However, monkeys will "pay" higher prices in lever presses for psychostimulants than they will for MDMA [99, 100]. Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may

develop ecstasy use or dependence [101, 102], though studies of non-representative samples have reported higher rates of dependence [103]. Most regular ecstasy users report taking ecstasy no more often than once a week [104]. Taken together, an examination of 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.

When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants, Liechti and colleagues stated that “none of the participants expressed any interest in taking MDMA as a recreational drug” after receiving MDMA in a controlled research setting, (p. 166) [61]. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions and memories related to the original traumatic incident in addition to or even instead of increased positive mood or euphoria. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings. Mithoefer reported that few participants in the study of MDMA-assisted psychotherapy in people with PTSD reported desiring to take MDMA in an unsupervised setting.

In the currently proposed protocol, diversion is not an issue because MDMA will only be administered under the supervision of the Principal 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.

7.4.6 Toxicity

The toxicity of MDMA has been investigated in numerous animal and in-vitro studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Finally, 28-day toxicity studies in canines and rodents have been performed [105], and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

Serious MDMA toxicity is rare even in uncontrolled settings, considering the millions of users taking ecstasy of unknown identity, potency, and purity [106-108], with many users consuming estimated MDMA doses that are several times higher than those used in the proposed program, without any apparent toxicity. Under unsupervised and nonmedical conditions, the most common SAE involves hyperthermia, described in Appendix A. In addition to hyperthermic syndromes, other rare AEs include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia, and these are described in more detail in the Investigator’s Brochure. The majority of ecstasy users visiting emergency departments do so because of anxiety or panic [109, 110]. In the proposed clinical protocol, study eligibility is intended to reduce the likelihood of many serious adverse events. Participants will be carefully monitored for signs and symptoms of these events and will be offered supportive psychotherapy and other forms of support determined to be

necessary by the Principal Investigator. Contingency plans for responding to these events are described in Appendix A.

7.4.7 Potential Neurotoxicity Associated with Ecstasy Use

Extensive studies in animals indicate that high or repeated doses of MDMA can damage serotonergic axons originating in the brainstem dorsal raphe nucleus, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site density [111-113], with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin [114]. Similar changes can be induced by methamphetamine and other psychostimulants [115-117]. Previous studies in nonhuman primates overestimated human-equivalent doses [118], and previous studies in rodents may also have overestimated human-equivalent doses [119]. Studies in rodents and monkeys that employed lower or fewer doses of MDMA, or that involved self-administration, have failed to find some or all of the markers of serotonin neurotoxicity listed above [96, 120-122]. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [123]. However, they are basing their case on studies that employed inappropriately high doses of MDMA, and studies comparing the effects of repeated use of ecstasy, often along with other drugs, as discussed below.

There is controversy as to whether analogous changes in brain serotonin occur in humans, and a wealth of literature exists that compares ecstasy users to non-users [124]. Earlier studies were retrospective and possessed a number of methodological flaws, particularly in relation to appropriate matching of ecstasy users with controls. Later research employed longitudinal study designs, allowing for comparisons over time. Retrospective and longitudinal imaging studies have detected decreased estimated serotonin transporter (SERT) sites in current heavy ecstasy users when compared with controls [125-127], but with estimated SERT sites returning to normal or numbers inversely related to period of abstinence. Likewise, studies have detected impaired memory and executive function in ecstasy users [124, 128, 129]. A number of these studies reported impaired cognitive function only in heavy users, and not in moderate users, and some recent studies suggest that use of other drugs may contribute to impaired cognition [130-133], though other studies also reported that abstinence from ecstasy did not attenuate memory impairment in heavy users [127, 134]. There is also some evidence that ecstasy users are more likely to report symptoms of anxiety or depression, and to exhibit more behavioral impulsivity than non-ecstasy user controls [135-138]. Findings from prospective and longitudinal studies suggest that young people with existing psychological problems are more likely to try ecstasy than people without these problems [101, 102], and it appears that polydrug use may contribute to this association [135, 138-140]. Findings from retrospective studies are of limited value in estimating the potential risk of neurotoxicity from two doses of MDMA, as average cumulative dose and frequency of use in most of these studies is considerably higher than doses in human trials of MDMA. A better estimate of the potential risk of neurotoxicity can be found in findings from prospective studies comparing people before and after their first use of ecstasy.

Starting in the early 2000s, a team of researchers in the Netherlands has examined

samples of people before and after reporting their first uses of ecstasy. These researchers have assessed estimated SERT sites, chemical markers of neuronal injury, changes in cerebral blood flow, performance and brain activity related to a working memory task, and cognitive function in samples of ecstasy users reporting an average use of 1 to 3 tablets [141-144]. The team also performed studies expressly in heavy ecstasy users [145-148]. They failed to find reductions in SERT sites, signs of neuronal injury or changes in performance on or brain activity during a working memory task in samples reporting use of no more than six ecstasy tablets [141, 142]. They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else, and they failed to find any markers of neuronal injury [141]. Low use of ecstasy also failed to alter brain activity or performance on a measure of working memory [116]. When comparing cognitive function in people before and after their first use of an average of 3.2 tablets, with non-user controls at similar points in time, ecstasy users showed less improvement on a memory task than non-users [141]. It is notable that the study examining SERT sites and cerebral blood flow did not employ non-user controls, that all participants in the study of cognitive function performed within the normal range, and that one individual had reportedly used ecstasy on 30 occasions rather than the limit of 10 occasions set for the other studies. Furthermore, there are some findings that women who decided to use ecstasy had higher impulsivity scores prior to use. [149]. Taken together, their findings fail to confirm serotonergic neurotoxicity after low ecstasy use, yet found some possible indications of impaired memory.

The risks of neurotoxicity are minimal in the proposed protocol. This is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. Nevertheless, the risks of neurotoxicity arising from MDMA administration will be described and noted in application materials prior to and during the completion of the application, and the investigators will informally monitor for any signs of changes in cognition after each MDMA-assisted psychotherapy session.

7.4.8 Reproductive and Developmental Risks

Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association, as discussed below in the "Pharmacology" section and in the Investigator's Brochure [150, 151]. Pregnant and lactating women will be excluded from participation in the proposed protocol, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to use birth control during the period of the protocol. If any participant becomes pregnant after the occurrence of at an experimental session, the sponsor and principal investigator will follow the pregnancy to outcome.

7.5 Medical Emergencies

The preparatory session, MDMA session and integrative session, 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 drugs 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 12-lead electrocardiogram (EKG) device, 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 pump will be used in place of intraarterial blood pressure monitoring equipment. For a recently completed Phase 2 trial, the researchers have established (in communication with the FDA) contingency plans for responding to those AEs that appear most likely, based on a comprehensive review of case reports of toxicity in illicit MDMA users reported by Baggott and colleagues in 2001 and in the current Investigator's Brochure. The same contingency plans and equipment will be used in this protocol, with the exception of the fact that there will not be an additional nurse on site for this study. In the unlikely event of cardiac arrest, the researchers 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 EMS, at which time 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.

8.0 Adverse Events

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 Common Expected Side Effects

Commonly expected side effects that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe. Common, expected side effects are defined as those most frequently reported in the literature and include: Anxiety, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Heavy Legs, Impaired Judgment, Impaired Gait/Balance, Increased Irritability, Increased personal worries or rumination, Insomnia, Jaw Clenching, Tight Jaw, Lack of Appetite, Low Mood, Nausea, Need More Sleep, Nystagmus, Parasthesias, Perspiration, Restlessness, Sensitivity to Cold, Thirst and Weakness. Other common side effects in preliminary data from the initial study of MDMA-assisted psychotherapy in people with PTSD include gastrointestinal discomfort or diarrhea in approximately 3.3% participants receiving MDMA.

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 a 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 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 within 24 hours or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitors:

Julie Holland, MD
NYU School of Medicine
200 East 33rd Street, Suite 16H
New York, NY 10016
(212) 358-5808 voice mail
jholland@inch.com

Study Monitor:

Berra Yazar-Klosinski PhD
Phone number: 831-429-6362
Fax number: 831-429-6370

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

- Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions from MDMA administration throughout the study
- Any event of concern to the participant throughout the protocol
- Any adverse event leading to withdrawal from the protocol
- Common expected side effects will be collected on the day of MDMA administration and for seven days after administration

9.0 Collection of Concomitant Medications

All medications, over the counter (OTC) and prescription will be collected from screening through 7 days after the last MDMA session. From 7 days after the last MDMA session through study termination only prescription or OTC medications taken to treat AEs will be collected.

Participant concomitant medications will be recorded during screening. If necessary, the investigators will make plans for tapering off and discontinuing any contraindicated medication at this time, in consultation with the prescribing physician. The investigators will request information about any changes in medication just prior to each MDMA-assisted psychotherapy session. Medications taken during the course of the protocol, including medications taken to treat AEs will be recorded on a concomitant medications CRF. Participants must be 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. They will be discontinued long enough before the MDMA session to avoid the possibility of interactions (the interval will be at least 5 times the particular drug's half-life). Participants 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). Participants must agree that, for one week preceding the MDMA session:

- a. They will refrain from taking any herbal supplement (except with prior approval of the research team).
- b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
- c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).

10.0 Clinical Laboratory Assessments

The Principal Investigator will examine laboratory assessments gathered in screening for assessing participant eligibility. The investigator will use a list of normal ranges to conclude whether participants are eligible for the protocol, and will indicate justification for admitting participants with abnormal values.

The following laboratory assessments will be performed as a part of screening:

Serum electrolytes and the **metabolic profile**, which includes:

ALT/SGPT;
albumin:globulin (A:G) ratio;
albumin, serum;
alkaline phosphatase, serum;
AST/SGOT;
bilirubin, total;
BUN;
BUN:creatinine ratio;
calcium, serum;
carbon dioxide;
chloride, serum;
creatinine, serum;
globulin, total;
glucose, serum;
potassium, serum;
protein, total, serum;
sodium, serum;

CBC, which includes:

Hematocrit;
hemoglobin;
MCV;
MCH;
MCHC;
RDW;
percentage and absolute differential counts;
RBC;
red cell count;
WBC;

Urinalysis, which includes:

Color;
appearance;
specific gravity;
pH;
protein;
glucose;
ketones;
occult blood;
leukocyte esterase;
nitrite;
bilirubin;

urobilinogen;

Thyroid function, which includes:

TSH high sensitivity;
Free T4;
Free T3.

In addition, **HIV and Hepatitis C** serology will be performed.

A urine-dip pregnancy test for females of childbearing potential will be performed as well.

The laboratory assessments other than the urine drug screen and pregnancy test will be performed at:

Laboratory Corporation of America
1280 Johnnie Dodds Blvd, Ste 108
Mount Pleasant, SC 29464

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

11.0 Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained prior to the start of the protocol. The clinical study 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. During each monitoring visit, source data verification will be performed by a Clinical Research Associate (CRA) to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the sponsor will be completed for each participant enrolled. Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

The sponsor will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

During or after the clinical protocol, 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 investigators will examine CAPS and GAF scores at baseline, one month after session 2, and two months after session 3 in active placebo, medium-dose and full-dose conditions. The investigators will record peak blood pressure, heart rate and body

temperature for participants during every session. Descriptive statistics will be calculated for all measurements overall and within the three dose conditions. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. Effect size of the three doses for all outcome measures for Stage 1, Stage 2, and one year post will be estimated using Cohen's techniques.

There will be preliminary examination of the data after all participants complete experimental sessions and the two-month follow-up, but before all participants have completed the 12-month follow-up. The interim data analysis will be conducted for safety and efficacy.

The sample selection is expected to produce acceptably homogeneous groups due to their all being veterans who served in the US Armed Forces diagnosed with PTSD and with CAPS scores of at least 50. 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, as depression.

Multivariate analysis of variance will be used to compare the full dose and non-full dose conditions for change in CAPS, BDI, PTGI-C and GAF scores. If a significant result is found, post hoc analysis of variance will be conducted for CAPS, BDI, PTGI-C and GAF scores separately. Further, if significant results are found for either CAPS, BDI, or GAF scores, post hoc t-tests will be conducted to determine explicitly where the differences occurred.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The investigators will informally or formally compare peak blood pressure, heart rate and body temperature for participants after sessions using active placebo, medium-dose and full-dose MDMA.

12.1 Statistical power

The literature does not provide an estimate of the effect size for change in CAPS after sessions using a medium-dose or for change in GAF scores under the proposed dosing regimen. The proposed study will provide these important estimates.

13.0 Informed Consent

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. Information about events during the MDMA session must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of evaluation, preparatory, MDMA and integrative psychotherapy sessions, the information should include that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to

applicable local regulations. The subject should have the opportunity to inquire about details of the MDMA session and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the investigator. The investigator will provide a copy of the signed ICF to the subject, and will maintain the original in the investigator's study file.

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 informed consent form, and written information should receive approval from an IRB before use.

Written consent to take part in the study session includes giving the investigators permission to view the participant's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

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

Participants can withdraw consent for participation in the protocol at any time without prejudice. If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization or equivalent form, MAPS will have full access to the 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.

13.1 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants in their role as research participants. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. Despite this, privacy cannot be guaranteed. Except for the screening log, the informed consent and a subject contact information sheet which will be stored separately from other documents, all data will be identified only by the participant's initials on the source document and three-digit subject number numeric code. If past medical records are needed participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. Copies of audio and video recordings intended for sharing with participants will only be marked with the participant's subject number. Any materials mailed to participants will be sent along with stamped return envelopes using the office address of the Principal Investigator both as main and return address. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators directly involved in the protocol, with

access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

All psychotherapy sessions will be recorded to video and audio. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted psychotherapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. Full names and addresses, if they appear in these recordings, will be edited out of the recording before the tape is seen by anyone other than the study participant, the investigators present at the session, and the designated audio/video technician who has signed a confidentiality agreement..

Any use of recordings for purposes other than research or training (eg: a documentary film) may occur only with separate written informed consent of the participant obtained after study participation is complete.

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. While it is possible that individuals may be identified on audiotape or video recording through means other than their names, restricting access to audio recordings or video recordings to researchers greatly reduces the risk of a breach of confidentiality.

13.2 Costs to Participants

There will be no costs to the study participants. The sponsor will cover all costs of study participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of the participant's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the participant or to the participant him or herself. It is anticipated that there will not be any charges for treatment that is unrelated to the study except in the case of participants who previously received therapy from the Principal Investigator and who will continue to receive ongoing treatment that is not related to participating in the study.

13.3 Treatment and Compensation of Study Related Injury

Treatment of a study-related emergency would first be billed to a participant's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a participant's health insurance. Most study-related emergencies can be treated by the investigators as described under "Medical Emergencies" (Section 7.5) and within Appendix A. If the investigator cannot treat a study-related emergency, then there are contingency plans for the transport of participants to the nearest hospital, East Cooper Medical Center.

14.0 Record Retention

Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS

representative before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained Record Retention Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records.

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Appendix A: Prevention and Response to Possible Serious Adverse Events

Risk Mitigation

Information from a considerable body of research indicates that the likelihood of significant toxicity from the doses of MDMA used in a therapeutic setting is very low [40], see also Section 6 of the “Investigator’s Brochure.” Psychiatrists in the U.S. and Europe reported administering MDMA to at least a thousand patients before the drug was made illegal without any drug-related SAEs occurring during sessions [33, 35, 58, 152, 153]. There have been no drug-related SAEs during the course of a study of MDMA-assisted psychotherapy in people with PTSD under the direction of the Principal Investigator for the proposed protocol, nor in any other ongoing sponsor-supported study of MDMA-assisted psychotherapy in people with PTSD.

Although serious untoward reactions are unlikely, the researchers will closely and continuously monitor participants during an experimental session. Throughout all sessions, participants will be attended by the investigators, a psychiatrist who is board-certified in emergency medicine and internal medicine as well as psychiatry and who maintains Advanced Cardiac Life Support (ACLS) certification, and a psychiatric nurse who will maintain Basic Life Support (BLS) certification. The Principal Investigator and assisting investigator will thus provide a team of an experienced emergency physician and a registered nurse to respond in the unlikely event of a medical emergency. In the unlikely event of cardiac arrest, they 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 EMS, at which time ACLS procedures will be instituted.

The listed means of minimizing the likelihood of any of the SAEs that are reported to occur in ecstasy users will be similar to the procedures and strategies employed in the current study of MDMA-assisted psychotherapy in people with PTSD.

Psychological Distress

Reports of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that some people receiving MDMA in a therapeutic context experienced periods of increased anxiety and even panic. In the proposed study, participants will have the intention of confronting and working on their traumatic experiences and accepting and working through difficult and painful emotions. Hence, signs of psychological distress, panic or other unpleasant psychological reactions are possible. Psychological distress could arise at any time after the onset of the effects of MDMA until the last effects have dissipated (approximately 3 to 5 hours after drug administration), with anxiety or distress potentially lasting for as little as 15 minutes to as long as 5 hours.

The potential for destabilizing psychological distress will be minimized in several ways. In several ways. During the preparatory sessions, participants will be made aware of the

fact that difficult emotions, including grief, rage and fear or panic, may arise during experimental sessions. Every effort will be made to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the session, including empathic listening on the part of the investigators and performance of diaphragmatic breathing by participants. Risks will be reduced by excluding people who might be more vulnerable to destabilizing psychological distress (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders), by preparing people before the experimental session, by creating an atmosphere of trust during the experimental session, by close monitoring, by daily contact with subjects for the period of a week after the experimental session, and by providing non-drug integrative psychotherapy sessions. Subjects will remain in the offices of the Principal Investigator for the evening and night immediately following each experimental session. The study site will be staffed by a trained attendant to respond to the needs of the subject. The investigators will offer specialized training for all attendants to prepare them for being supportive but not intrusive as subjects rest and reflect on the day's experience. The attendant will be instructed to contact the investigator upon request or at the appearance of signs of a potential adverse event. The overnight stay in a private room in the study site and the presence of the attendant should further reduce psychological distress. There is also the possibility of psychological distress during the integration period following experimental sessions unrelated to direct effects of the experimental compound. Such distress occurs commonly in Prolonged Exposure, EMDR and other therapies for PTSD.

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

- If the participant is anxious, agitated, in danger of any self-harm or is suicidal at the end of the MDMA session, the investigators will remain with the participant for at least two more hours. During this time, the investigators will employ affect management techniques, will talk with the participant to help them express their feelings or gain cognitive perspective of their experiences, and will help them implement the self- soothing and stress inoculation techniques presented during the introductory session. If this situation should occur during an integrative therapy session, at least one of the investigators will be available to stay with the participant for at least two additional hours.

- If a participant 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 Principal Investigator will decide between one of two options:

- A. A psychiatric nurse, therapeutic assistant or therapist will stay with the subject until the time of his or her appointment with investigators the next day. The investigators will then meet with the subject daily until the period of destabilization has passed. At any time during this process, the Principal Investigator may make the clinical judgment to proceed to option B.

B. Hospitalization for stabilization.

Participants hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the investigator will carefully evaluate the participant's emotional status. The investigators will submit an SAE report to the IRB and the FDA in cases of drug-related hospitalization.

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

The investigators have developed a contingency plan for responding to suicidal intent. They will evaluate the degree of suicidal intent and take steps to alleviate psychological distress.

Seriousness of suicidal intent would first be evaluated by the investigators both clinically and through administrations of the CSSRS. Depending upon what is learned from evaluation, the investigator might increase support for and discussion with the participant, increase frequency of contact, or if during an experimental session, remain with the subject. Hospitalization would be considered in some situations as described in Appendix A on p. 61.

If the participant exhibits signs of suicidality the investigators will also call the contact person designated by the subject.

The investigators will use the same procedures for all participants whether they are within or beyond reasonable driving distance from the study site. Increased telephone contact could be used if additional appointments were not a viable option for a participant not within easy driving distance of the site. The treating therapist of any participant living outside reasonable driving distance would be enlisted to provide evaluation and support for the participant.

In the event of a participant's experiencing severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an MDMA session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." This medication will be captured on a psychotropic concomitant medications CRF page. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Means of monitoring for and preventing possible risks of MDMA other than the cardiovascular risks and psychological distress are described in detail below.

Angina or Myocardial infarction

If a participant experiences ischemic type chest pain, whether or not it is 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 given 162 mg of chewable aspirin once 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 individuals who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have EKG evidence of AMI [154].

Stroke

If any participant has neurologic 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 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 [155, 156].

Hyponatremia

History of hyponatremia or detection of hyponatremia on initial laboratory examination will be cause for exclusion from the proposed protocol. Participants will be given primarily electrolyte solutions such as Gatorade instead of water in order to decrease the likelihood of dilutional hyponatremia. They will not be allowed to drink more than 3 L of fluids, and fluid intake will be appropriately spread out across the session. If there are any signs or symptoms of hyponatremia, a stat serum sodium will be drawn and fluids will be withheld until the results are obtained. If the serum sodium is less than 125mEq/L, serum and urine osmolality and sodium will be measured, and the subject will be transported to the East Cooper Medical Center, where further intervention can be provided.

Hyperthermia

Body temperature will be taken every 60 to 90 minutes throughout each experimental session. If temperature rises more than 1° Celsius (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 subject. 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, creatine phosphokinase (CPK), prothrombin time (PT), partial thromboplastin time (PTT), platelets and liver enzymes, and urine will be collected for urinalysis. If there are significant abnormalities in these tests, if the temperature continues to rise, or if an elevated temperature is

associated with delirium or muscle rigidity the participant will be transferred to the intensive care unit at the East Cooper Medical Center.

Appendix B: Audio and Video Recording

Recording to video will be done with two cameras operated remotely by the investigators, already present as co-therapists for the experimental and non-drug psychotherapy sessions. One camera will be adjusted to capture a fairly tight shot of the subject, including full-face shots and partial or full body shots. The other will capture a wider view including the subject and the two investigators. Two copies of the video will be made routinely, one to be stored by the investigators, and the other by the sponsor. Both will be kept in locked cabinets in secure locations. A third copy of any video recording can be made for any subject who requests it.

Full names and addresses are unlikely to appear on the video or audio tapes. However, if they do, they will be edited out of the recording before the tape is seen by anyone other than the study participant and the investigators present at the session. Facial images will not be removed from the copy of the video recording to be viewed by the sponsor or investigators for review of the therapeutic process and for manual development.

Audio recording of experimental and non-drug psychotherapy sessions will be done using a digital recording device controlled by one of the investigators, with control allowing him to stop or start recording. The recordings will be transferred to an external hard drive that will be kept in a locked cabinet. The recordings will then be burned onto CDs. One copy will be stored by the investigators in a locked cabinet, another copy will be sent to the sponsor and will also be stored in a locked cabinet at the location of the sponsor. An additional audio recording can be made of any psychotherapy session. The purpose of this is to enable the participants to have a recording for themselves at the end of each experimental session, rather than having to wait until the CDs are made by the investigators. Part or all of these recordings may be viewed by people training to perform MDMA-assisted psychotherapy for sponsor-supported studies.