PROTOCOL MP-8

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A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)

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1.0 List of Abbreviations

ACLS	Advanced cardiac life support
AE(s)	Adverse Event(s)
AED	Automated External Defibrillator
A:G	Abumin : Globulin ratio
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI-II	Beck Depression Inventory-II
BLS	Basic Life Support
BP	Blood Pressure
BT	Body Temperature
BUN	Blood Urea Nitrogen
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
DES-II	Dissociative Experiences Scale II
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
ECG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
F	Fahrenheit
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
LSD	d-lysergic acid diethylamide

MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
NEO PI	Neuroticism-Extroversion-Openness Personality Inventory
NK	Natural Killer
OTC	Over the counter (non-prescription)
PSQI	Pittsburgh Sleep Quality Index
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTGI	Post Traumatic Growth Inventory
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-I-RV	Structured Clinical Interview for Diagnoses Axis I Research Version
SERT	Serotonin Transporter
SOCQ	States of Consciousness Questionnaire
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
Stage 1	Randomized, double blind study arm
Stage 2	Open-label, partial crossover study arm
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 another Phase 2 study in Switzerland. An additional Phase 2 study is planned to start in the near future in Canada, with approval from Health Canada and a Canadian Institutional Review Board (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 twenty-four veterans, firefighters or police officers with service related PTSD, and will seek to enroll roughly equal numbers of men and women. This study will include those with chronic PTSD of at least six months duration who satisfy PTSD diagnostic criteria despite having received prior treatment with either medication or psychotherapy. Full, medium and low dose MDMA will be assessed in Stage 1, as well as the benefit of three vs. two full dose sessions. Subjects who received the medium and low dose during Stage 1 will have the opportunity to cross over and take part in a second study segment, referred to as Stage 2, with three open-label experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

MAPS' initial U.S. pilot study enrolled 21 subjects, a majority (17) of whom were women suffering from PTSD related to sexual assault and/or childhood sexual abuse[1, 2] . Only two subjects had PTSD from war-related trauma (U.S. veterans of the Iraq War) and both were male. According to the European Medicines Agency (EMEA) Guideline for the Development of Medicinal Products for the Treatment of 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, firefighters and police officers with service related trauma will be compared with results from our initial U.S. pilot study, mostly in women survivors of sexual abuse and assault.

In order to refine our triple-blind methodology, the proposed study will also evaluate three different doses of MDMA to determine their relative success in achieving blinding of 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 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% [3]. Combat exposure can produce a form of PTSD that is "chronic, disabling and highly comorbid." [4, 5], and that can be especially resistant to pharmacotherapy with Selective Serotonin Reuptake Inhibitors (SSRIs) [6]. PTSD is common in other countries as well [7-11]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [12], and it is estimated that the number of service members returning home from the Iraq and Afghanistan wars with PTSD will be between 75,000 and 225,000 [13]. 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 [14]. 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 [15-17]. PTSD is typically a chronic illness [18, 19], associated with high rates of psychiatric and medical co-morbidity, disability, suffering and suicide [9, 18, 20, 21]. During an appearance at a gathering of mental health professionals on October 26, 2009, U.S. 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." [22]

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 [23, 24], 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 [25]. 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" [26].

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 [27, 28] and D-cycloserine-assisted psychotherapy [29]. 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 [30]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [31]. 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 [32].

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 [33-38]. 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 U.S. 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 they can arrest and reverse the hippocampal atrophy found in PTSD patients [39]. 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 be effective in this way. 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 [40]. 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 [41, 42].

2.4 Previous MDMA Research

As of June 2011, MDMA has been administered to approximately 540 research participants, in both Phase 1 and Phase 2 studies, without any occurrences of drug-related Serious Adverse Events (SAEs) [43-56].

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 studies taking place in the U.S., Canada and Israel. The lowest initial and supplemental doses (30 and 15 mg) are only five milligrams above the lowest dose (25 mg) 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 [33] and a series of basic research studies occurring in the Netherlands [e.g. 51, 57]. The addition of a supplemental dose half the size of the initial 75 mg dose produces a total dose of 112.5 mg, which is below the dose used in the first U.S. investigation of MDMA-assisted psychotherapy.

3.0 Protocol Objectives

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

3.1 Primary Objective

- Assess changes in PTSD symptoms via Clinician-Administered PTSD Scale (CAPS) global scores in participants receiving by condition in the randomized study arms at baseline and the primary endpoint, one month after the second experimental session.

3.2 Secondary Objectives

The following objectives will compare full, medium and low dose subjects in the blinded portion of Stage 1:

- Assess changes in posttraumatic growth via Post Traumatic Growth Inventory (PTGI) scores from baseline to the primary endpoint.
- Assess changes in global functioning via Global Assessment of Functioning (GAF) scores from baseline to the primary endpoint.
- Assess changes in symptoms of depression via Beck Depression Inventory-II (BDI-II) scores from baseline to the primary endpoint.
- Assess changes in self-reported sleep quality via the Pittsburgh Sleep Quality Index (PSQI) from baseline to the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociative Experiences Scale II (DES-II) from baseline to the primary endpoint.
- Assess changes in Neuroticism-Extroversion-Openness Personality Inventory (NEO PI) scores from baseline to the primary endpoint.

The following objectives will compare effects in specified subjects:

- Assess PTSD symptoms via CAPS, posttraumatic growth via PTGI, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, dissociation symptoms via DES-II, and personality via NEO PI throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of receiving active dose MDMA on PTSD symptoms via CAPS, posttraumatic growth via PTGI, personality changes via NEO PI, depression symptoms via BDI-II, global functioning via GAF, and sleep quality via PSQI one year after the final experimental session for each participant.

The following objectives will include exploratory analyses intended to inform protocol design:

- Explore the effects of each MDMA-assisted psychotherapy session upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Assess the effects of a third active dose experimental session by comparing Global CAPS, BDI-II, GAF, PSQI, PTGI (in reference to start of the study), and

DES-II scores at the primary/secondary endpoint and end of Stage 1/ Stage 2 in subjects receiving a third experimental session in Stage 1 and Stage 2.
- Assess the ability of the investigators and participants to accurately guess condition assignment when asked to do so after each blinded experimental session.
- Assess value of third experimental session in Stage 1/Stage 2 by collecting each active dose subject's perception of experimental sessions at the primary/secondary endpoint and end of Stage 1/ Stage 2.
- Correlate adherence to the Treatment Manual with Global CAPS scores using adherence criteria ratings to assess videos of psychotherapy sessions.

3.3 Safety Objective
To monitor and ensure safety of participants during and after experimental sessions by assessing physiological effects, psychological effects, adverse events, spontaneously reported reactions and suicidality.

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) before, during and after experimental sessions and on selected days of telephone or face-to-face contact, with comparisons made between subjects in each condition.
- Subjective Units of Distress (SUD) and vital signs (blood pressure, heart rate and temperature) will be measured during each experimental session, and comparisons will be made for vital signs between conditions.
- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.
- Serious adverse events, adverse events and spontaneously reported reactions will be collected during the study according to Section 8.

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. See Section 4.6 below for more information.

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 [58, 59]. In the first completed study of MDMA-assisted psychotherapy in people with PTSD, the Clinical Investigator of this protocol reported a significantly greater reduction in PTSD symptoms, as assessed by an independent rater, in people who received MDMA with psychotherapy compared to those who received placebo and the same psychotherapy [1]. Placebo-controlled clinical trials have

confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion [60-67]. Effects in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with Ecstasy (see for example [60] versus [68]). 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 [69-71]. Its direct actions on serotonergic, adrenergic and other receptors are considerably weaker.

4.3 MDMA Doses, Compounding, and Labeling

The study will employ three different dosage levels, with the lowest dosage considered low dose and the highest dosage level considered a full dose. All participants will receive an initial dose, and 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.

This protocol will follow a randomized, triple-blind, dose response design that will compare three doses of MDMA. The initial doses are 30 mg for low dose, a medium dose of 75 mg, and a full dose of 125 mg. Twelve participants will receive an initial dose of 125 mg of MDMA followed by an optional supplemental dose of 62.5 mg. Six participants will receive an initial dose of 75 mg MDMA followed by an optional supplemental dose of 37.5 mg, and six participants will receive an initial dose of 30 mg followed by an optional supplemental dose of 15 mg.

Table 1. Stage 1 Blinded Drug Doses for MP-8

Condition	**Number of Subjects**	**Initial Dose**	**Supplemental Dose**	**Min-Max Cumulative Dose**
Low Dose	6	30 mg	15 mg	30-45 mg
Medium Dose	6	75 mg	37.5 mg	75-112.5 mg
Full Dose	12	125 mg	62.5	125-187.5 mg

Table 2. Stage 2 Drug Doses for MP-8

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose	Min-Max Cumulative Dose with Titration
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

The full MDMA dose to be used in this study is identical to those used in previous studies in the U.S., Switzerland, and Israel. Previous researchers have also used doses within this range [44, 51, 60-62, 65, 72-75]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [36, 37, 58]. The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD.
The initial full dose is expected to produce all the commonly reported effects of MDMA, including changes in affect, mood, and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose.

The 100mg MDMA initial dose will be administered in the first experimental session in Stage 2 to enable a comparison of subjective and therapeutic effects to full dose MDMA. Prior to both the second and 3rd experimental sessions in Stage 2 the co-therapists, in consultation with the subject, will decide whether the same dose or an initial dose of 125mg (each with the corresponding optional supplemental dose) would be more likely to constitute the optimal therapeutic dose for each of these experimental sessions.

MDMA in bulk will be sent from Organix Inc., in Woburn, MA, to the Clinical Investigator, who has been issued the Schedule 1 license by the Drug Enforcement Agency (DEA). The Clinical Investigator and unblinded Randomization Monitor will oversee compounding by a pharmacist in a manner that will maintain the blind for the Clinical Investigator. The pharmacist will provide bulk lactose for compounding MDMA capsules. The pharmacist will weigh the MDMA into doses of 125, 100, 75, 62.5, 50, 37.5, 30, 25 and 12.5 mg (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules in combination with lactose used to ensure that all blinded capsules have similar appearance and weight. Capsules for the initial dose will be a different color from capsules used for the supplemental dose. All capsules will be compounded so that they weigh the same amount, but contain varying amounts of MDMA and lactose. Capsules for all experimental, triple-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of blinded capsules. Dosage for open-label sessions will be clearly indicated in the packaging.

Doses of MDMA for each experimental session will be stored in separate primary containers labeled with the protocol number, drug name, lot number, unique container number, sponsor name and a statement that the drug is for clinical trial use only. Labels for each container of MDMA will be provided by the sponsor and applied by the pharmacist. The contents of the blinded primary containers will be hidden from the investigator to assure blinding.

Figure 1. Examples of Blinded Labels

Holding Box Labels

Box Label
MAPS Study# MP-8
Investigational Product: MDMA
Dose: XXXmg
Lot #: XXXXX
Administer as per protocol
Caution-Limited by Law to Investigational Use Only

Stage 1 Primary Container Labels

Blinded Labels	Open Label Session 3 Labels
MAPS Study MP-8 Experimental Session #__ Container # XXX Subject #_____ Administer as per protocol Investigational Use Only	MAPS Study # MP-8 Experimental Session #____ 125 & 62.5mg Container # XXX Subject #_____ Administer as per protocol Investigational Use Only

Stage 1 Inner Envelope Labels

Blinded

Stage 1 Container # XXX
INITIAL DOSE
Subject #_____Ex. Ses # _____

Blinded

Stage 1 Container # XXX
SUPPLEMENTAL DOSE
Subject #_____Ex. Ses # _____

Open Label Session 3

Stage 1 Open Label 125mg
INITIAL DOSE
Subject #_____Ex. Ses # _____

Open Label Session 3

Stage 1 Open Label 62.5mg
SUPPLEMENTAL DOSE
Subject #_____Ex. Ses # _____

Stage 2 Primary Container Labels

Open Label Session 1 Open Label Session 2 or 3

MAPS Study # MP-8 Stage 2 100mg & 50mg MDMA Lot # XXX Container # XXX Subject #_____ Experimental Session #1 Administer as per protocol Investigational Use Only	MAPS Study # MP-8 Stage 2 100+25mg & 50+12.5mg MDMA Lot # XXX Container # XXX Subject #_____ Experimental Session #___ Administer as per protocol Investigational Use Only

Stage 2 Inner Envelope Labels

Open Label Session 1	Open Label Session 1
Stage 2 Open Label 100mg INITIAL DOSE Subject #_____Ex. Ses # 1	Stage 2 Open Label 50mg SUPPLEMENTAL DOSE Subject #_____Ex. Ses # 1
Open Label Session 2 or 3	**Open Label Session 2 or 3**
Stage 2 Open Label 100mg INITIAL DOSE Subject #_____Ex. Ses #___	Stage 2 Open Label 50mg SUPPLEMENTAL DOSE Subject #_____Ex. Ses #___
Stage 2 Open Label 25mg INITIAL DOSE Subject #_____Ex. Ses #___	Stage 2 Open Label 12.5mg SUPPLEMENTAL DOSE Subject #_____Ex. Ses #____

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with federal and state regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled "inner envelopes" within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

4.4 MDMA Accountability

Forms will be provided to track drug accountability and administration throughout the study. Blinded drug accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all state and federal regulations and forms pertaining to the use of controlled substances, and forms will be maintained by the Schedule 1 License Holder.

Each primary container label will contain a unique container number for the drug assigned to a single experimental session. The container numbers will be used to track drug administration in the Source Record and the drug administration log. The web-based randomization system will enable tracking of blinded primary containers for drug accountability purposes.

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 DEA requirements, the Clinical Investigator will be responsible for storing and dispensing the MDMA. It will be stored in a safe mounted to the floor that has been inspected and approved by the DEA for this purpose. Only the Clinical Investigator with the Schedule 1 license will have the combination to the safe. The room in which the safe is mounted has an alarm system and will be locked whenever the CI or his staff are not present.

All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each experimental session. Supplemental doses are provided for each experimental session but are optional to use. In addition, the clinical titration doses with corresponding supplemental dose are provided in Stage 2 session 2 and 3 and their use is optional.

The Schedule 1 License Holder will dispense the appropriate container number for each experimental session. If an optional dose is not administered the unused capsules will be kept in their respective inner envelopes inside of the primary container in the safe for drug accountability.

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 in a locked office with an alarm system.

4.6 MDMA Stability

Complete details on the chemistry, manufacturing and control of the MDMA 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 U.S. pilot study of MDMA-assisted psychotherapy in people with PTSD. The analysis found the MDMA to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart on February, 2006, continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9% pure. This MDMA was used in an investigation of MDMA-assisted psychotherapy that took place in the U.S. with drug administration ending in 2008, and it was also used in non-sponsor supported study in 2006[76].

5.0 Protocol Design

This randomized, triple-blind study will examine the safety and efficacy of MDMA-assisted psychotherapy with 30, 75 or 125 mg MDMA in twenty-four veterans, firefighters and police officers diagnosed with chronic, treatment-resistant PTSD arising from their service. These participants will ideally, but not necessarily, include twelve men and twelve women. 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 non-drug psychotherapy sessions with a male and female co-therapist team. Stage 1 of the study will consist of two blinded experimental sessions and, for the full dose group, one open-label experimental session, each lasting six to eight hours and scheduled three to five weeks apart. The study will be unblinded after the second experimental session in Stage 1, which constitutes the primary endpoint assessment. After unblinding, medium dose and low dose subjects will have the opportunity to continue to open-label Stage 2, unless they meet any exclusion criteria for study participation and full dose subjects will complete the third open-label experimental session. All subjects will complete a long-term follow-up visit 12 months after their final experimental session. All psychotherapy sessions may be recorded to audio and video. In the first open-label experimental session in Stage 2, subjects will receive 100mg with an optional supplemental dose of 50mg. In the second and third open-label experimental session in Stage 2, subjects will receive one of two active doses of MDMA that are clinically titrated by the CI. Experimental sessions will otherwise follow the same sequence of events after a single preparatory session. (See Time and Events Table).

A co-therapist team will perform all non-drug and MDMA-assisted psychotherapy sessions in their outpatient office. Participants will complete the SOCQ, a measure of alterations in consciousness related to mystical experiences, during the period of time between the end of each MDMA-assisted psychotherapy session and before they leave the treatment facility the next day. Participants will remain at the study site overnight accompanied by an 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.

A blinded independent rater, who will not be present during any psychotherapy sessions, will assess participant PTSD symptoms with CAPS, symptoms of depression with BDI-II, posttraumatic growth with PTGI, global functioning with GAF, sleep quality with PSQI, and dissociation with the DES-II. Changes in personality traits will be assessed via NEO-PI. Outcome assessments will be done at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at the 12-month follow-up and at equivalent points in Stage 2.

When each subject completes the evaluation at the primary endpoint, the blind will be broken for that subject. Participants who had been assigned to receive low dose or medium dose MDMA will subsequently have the opportunity to enroll in the open-label study arm, or "Stage 2." Stage 2 must start within a maximum of 5 months after the participant finishes Stage 1. The open-label study arm will follow a similar sequence of events and procedures, except that there will be a single preparatory session, and all three MDMA-assisted psychotherapy sessions will be open-label. Subjects will receive an initial dose of 100 mg MDMA in the first experimental session, and one of two active doses of MDMA that are clinically titrated by the CI during the second and third open-label experimental sessions that will otherwise follow the same sequence of events (See Time and Events Table). Outcome measures except for the NEO PI will be repeated one month after the second Stage 2 experimental session, and all outcome measures will be repeated at the end of Stage 2.

The study will conclude with a one-year follow-up occurring 12 months after the final experimental session of Stage 1 for participants who received full dose MDMA or who elected not to enroll in Stage 2 after receiving either the medium or low doses in Stage 1. Subjects who enrolled in Stage 2 will have their final follow-up 12 months after the final open-label experimental session. Outcome measures will be repeated at the 12-month follow-up, as well as a questionnaire concerning self-reported long-term effects of study participation.

An interim analysis may be performed before all participants have completed the 12-month follow-up. The interim data analysis may be conducted for safety and efficacy.

Sub-studies in a select group of subjects in this study may be conducted for exploratory purposes. Subjects will complete a separate consent process if they chose to participate in these studies.

5.1 Planned Duration of Protocol

Stage 1 will take up to six months (full dose group) or four months (medium and low dose groups) to complete after screening and baseline evaluation. The screening and baseline evaluation can take up to 4 months. In addition, if the length of time between the end of tapering and the first experimental session is longer than a month, the CAPS should be repeated to show consistency between this score and the baseline CAPS. The open-label study segment for participants initially assigned to receive low dose or medium-dose MDMA (Stage 2) will last an additional five months from the single introductory and review psychotherapy session until the evaluation two months after the final open-label MDMA-assisted psychotherapy session. The time period between the end of Stage 1 and the start of Stage 2 should not exceed 5 months for any participant with CAPS re-assessment done if there is an interval of greater than 8 weeks between the end of Stage 1 and the beginning of Stage 2. The 12-month follow-up will occur a year after the final experimental session for all participants who complete Stage 1 only, and a year after the final open-label session for any participants who enroll in and complete

Stage 2. For each participant who enrolls only in Stage 1, the entire study duration will be up to 1.5 years including the 12-month long-term follow-up, and for the participants that complete both Stage 1 and Stage 2 follow-ups, the study may take about two years.

5.2 Randomization and Subject Numbering

This is a randomized, triple-blind, dose comparison study with an open-label cross-over segment. For Stage 1, a randomization list will be prepared at the beginning of the study. Another list will be created to replace subjects who withdraw from the study and are unblinded. Each participant will be assigned to one of the three dose conditions; 30 mg (low dose), 75 mg (medium- dose) or 125 mg (full dose). Twelve participants will be assigned to the full-dose condition, six participants to the 75 mg condition and six participants to the 30 mg low dose condition. The study will employ a blinded randomization procedure that will maintain the 2:1:1 ratio while maintaining the blind and ensuring that each subsequent condition assignment is not predicated on the previous assignment. Drug containers will be assigned a unique random number. At least 24 hours before each experimental session, container assignments to each subject will be performed on a per experimental session basis, and the container will contain the initial and supplemental capsules for a single experimental session. This will be done by contacting the Randomization Monitor or logging into the web-based randomization system. The unblinded Randomization Monitor will also oversee drug encapsulation and labeling of drug bottles. Replacement doses for subjects who replace dropouts that retain the same ratio of condition assignment will also be created. The Randomization Monitor will provide the investigators with sealed envelopes that will permit emergency unblinding for an individual subject if required. In all other cases, the blind will be maintained up through the primary endpoint assessment. The participant, independent rater and both investigators conducting psychotherapy will be blind to condition assignment, until that point. Participants who drop out of the study or are withdrawn by the Clinical Investigator prior to the primary endpoint will be replaced until blinded data has been collected from 24 participants. Subjects who withdraw during Stage 2 or during the long-term follow-up portion of the study will not be replaced.

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 24 veterans, firefighters or police officers with chronic, treatment-resistant, PTSD arising from their service. Treatment resistance is defined as PTSD of at least six months duration where patients were unable to achieve remission despite having received prior treatment with either pharmacotherapy or psychotherapy of adequate dose/duration or who discontinued treatment due to lack of

tolerability. Of the 24 subjects to be enrolled in this study, at least 18 must have PTSD of less than 10 years duration (from Iraq and Afghanistan Wars) while up to 6 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, fire or police service was 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 twelve men and twelve women. Subjects of each sex who qualify and agree to participate will be accepted into the study in chronological order until twelve subjects of either sex have been enrolled. Enrollment will then be limited to members of the opposite sex until twelve male and twelve female subjects have been enrolled. If, however, attempts to recruit equal numbers of male and female subjects turns out to result in 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 24 participants.

Participants will be recruited via letters of referral sent to psychiatrists and psychotherapists, contact with veterans' organizations, written advertisements, announcements placed on appropriate internet sites and the sponsor website, 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 that 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 electronically. If, after review, a potential participant remains interested in taking part in the study, then he or she will meet with the investigators to complete the consent process. Participants 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. Be diagnosed with chronic PTSD, duration of 6 months or longer resulting from traumatic experience during military service;

2. Have a CAPS score showing moderate to severe PTSD symptoms;

3. Have had at least one unsuccessful attempt at treatment for PTSD either with talk therapy or with drugs, or discontinuing treatment because of inability to tolerate psychotherapy or drug therapy.

4. Are at least 18 years old;

5. Must be generally healthy;

6. Must sign a medical release for the investigators to communicate directly with their therapist and doctors;

7. Are willing to refrain from taking any psychiatric medications during the study period;

8. Willing to follow restrictions and guidelines concerning consumption of food, beverages, and nicotine the night before and just prior to each experimental session;

9. Willing to remain overnight at the study site;

10. Agree to have transportation other than driving themselves home or to where they are staying after the integrative session on the day after the MDMA session;

11. Are willing to be contacted via telephone for all necessary telephone contacts;

12. Must have a negative pregnancy test if able to bear children, and agree to use an effective form of birth control;

13. Must provide a contact in the event of a participant becoming suicidal;

14. Are proficient in speaking and reading English;

15. Agree to have all clinic visit sessions recorded to audio and video

16. Agree not to participate in any other interventional clinical trials during the duration of this study.

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

1. Are pregnant or nursing, or if a woman who can have children, those who are not practicing an effective means of birth control;

2. Weigh less than 48 kg;

3. Are abusing illegal drugs;

4. Are unable to give adequate informed consent;

5. Upon review of past and current drugs/medication must not be on or have taken a medication that is exclusionary.

6. Upon review of medical or psychiatric history must not have any current or past diagnosis that would be considered a risk to participation in the study.

6.0 Methods

The following outcome, safety and process measures will be used in the study. Investigators will follow the most recent version of the Treatment Manual in all matters relating to the psychotherapy sessions and follow-up. All psychotherapy sessions, including experimental sessions, may be recorded to audio and video, with all recordings preserved for research and training purposes.

After consenting to take part in the study, 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 electrocardiogram (ECG), and if the Clinical 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 I Research Version (SCID-I-RV) to assess eligibility based on Axis I diagnoses, and relevant parts of the Axis 2 SCID, which includes a self-report questionnaire to focus on modules to use

based on symptoms 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 enroll the subject in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

After undergoing three 90-minute non-drug introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo eight-hour long experimental sessions scheduled approximately three to five weeks apart, during which they will randomly receive either the low dose, medium-dose or full-dose MDMA on all three occasions. Participants will undergo one non-drug integrative psychotherapy session the day after each experimental session and at least two additional 90 minute non-drug integrative psychotherapy sessions between experimental sessions.

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 believe they received. The rater will assess PTSD symptoms, global functioning, dissociative symptoms, sleep quality, symptoms of depression and post-traumatic growth prior to MDMA-assisted psychotherapy at baseline, one month after the second experimental session and, for full dose subjects, two months after the third experimental session. Personality will be assessed at baseline, at the primary endpoint, at the end of Stage 2, and at 12-month follow-up. Alterations in consciousness and elements of a mystical experience will be assessed after each MDMA-assisted psychotherapy session before the subject leaves the treatment facility the following day. All psychotherapy sessions, including MDMA-assisted experimental sessions, may be recorded to audio and video, with all recordings preserved for research purposes. Participants may receive any session recordings upon request. Participants will be asked to read a brief script for a computer program that will enable transcription of audio recordings from these sessions.

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 similar sequence of events to the full dose subject group in Stage 1, 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 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 [78, 79]. An independent rater will assess all participants according to the Time and Events table.

The Global Assessment of Functioning (GAF) is a measure of global functioning 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 according to the Time and Events table.

The Beck Depression Inventory-II (BDI-II) is a 21-item a self-report measure of depressive symptoms [80] that will serve as a measure of depression. It takes five to ten minutes to complete. Participants will complete the BDI-II according to the Time and Events table.

The Post Traumatic Growth Inventory (PTGI) 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. In this study, participants will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions. Participants will complete the PTGI according to the Time and Events table.

The DES-II is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual’s thoughts, feelings, or experiences into the stream of consciousness or memory [81, 82]. It is an established measure of dissociative symptoms. The scale consists of statements describing facets of dissociation. Respondents indicate how often the specific experience happens to them, from “never” to “always.” Responses on the original scale were made via visual analog scales. The DES-II uses the same items but with responses made on a ten-point scale from “0%” to “100%” of the time. The scale is scored by treating percentages as single digits to produce a total score. The DES-II can also be used to produce scores for three factors, amnesia, depersonalization, and derealization. The scale differentiated between respondents without psychiatric disorders or with psychiatric disorders with few dissociative symptoms and respondents with psychiatric disorders associated with dissociative symptoms [81]. Reliability of the DES-II is high (ranging from 0.79 to 0.96 in an early review), and a reported Cronbach’s alpha

of 0.95 [82, 83]. There may be a relationship between experiencing dissociation and occurrence of chronic PTSD [82, 84].

The Pittsburgh Sleep Quality Index (PSQI) is a measure of self-reported sleep quality over a one month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. It consists of 19 items, with possible responses ranging from 0 to 4 on a five-point scale [85]. The PSQI consists of seven sub-scales: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. These are all summed to produce a single global scale. Global scores can range from 0 to 21, with higher scores reflecting poorer sleep quality, and a score below 5 indicative of good sleep. It takes five to ten minutes to complete. Test-retest reliability ranges from 0.85 to 0.87, and it is internally consistent, with a Cronbach's alpha of 0.83[85, 86]. Global scores correlate with other measures of alertness and self-reported sleep quality [87]. PSQI will be administered according to the Time and Events table.

The NEO PI will serve as a measurement of personality [88]. The NEO PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model. Participants will complete the NEO PI according to the Time and Events table.

The States of Consciousness Questionnaire (SOCQ) is a 100-item questionnaire based on the "Peak Experience Profile" designed by Pahnke and colleagues [89, 90]. Participants respond to the SOCQ using a six-point Likert-type scale anchored at 0=none at all and 5=extreme (more than ever before in my life). It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. The measure is a self-report instrument and takes approximately 20 to 30 minutes to complete. Participants will complete the SOCQ after each experimental session in accordance with the Time and Events table, completing the measure at any time between the end of an experimental session and prior to leaving the treatment facility the next day.

The long-term follow up questionnaire has been developed internally by the Sponsor to assess long-term benefits and harms of MDMA-assisted psychotherapy at the 12 month follow up visit. This questionnaire takes between five and ten minutes to complete.

6.1.2 Safety Measures

Safety measures will be applied as described below to minimize risks associated with drug-assisted psychotherapy sessions.

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.

Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure, heart rate (as pulse) and temperature will be measured 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 measurements will be taken as per the judgment of the Clinical Investigator. Blood pressure and pulse will be assessed via an automatically inflating cuff. Body temperature will be assessed via tympanic thermometer every 60-90 minutes. For subjects with a diagnosis of pre-existing controlled hypertension, the results of blood pressure and pulse measurements will be viewed by the investigators as the measurements occur. For subjects without a diagnosis of controlled hypertension, after viewing baseline values at the beginning of the session, the investigators will only view the blood pressure or pulse values in the case of a medical indication in order to improve the effectiveness of condition blinding. The night attendant will print out the blood pressure and pulse results after the session, make a back-up copy, and will seal both copies together in an envelope and write their initials over the seal. This envelope will be part of the source record and will be kept sealed until after unblinding occurs for that subject. In the event of any medical indication, such as signs or symptoms that could be related to either hypertension or hypotension, the investigators have the option to print out the results during the session.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [91]. 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 by the investigators in accordance with the Time and Events table. The measure will be administered at baseline, during the second preparatory session, twice during experimental sessions (once before and once after drug administration), on two days of telephone contact, during each integrative psychotherapy session and at the evaluation at the end of Stage 1, end of Stage 2 and the 12-month follow-up. Participants undergoing medication washout will complete the C-SSRS before and after medication washout.

A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain [92-94]. The Changes in Tinnitus and/or Pain visual analog scale will allow rating of symptom severity from "None" to "Worst Case

Imaginable". This exploratory measure will enable quantification of subjective somatic symptoms that are known to be associated with PTSD [93, 95-97]. Presence of chronic pain is associated with PTSD, possibly as a result of psychological response to traumatic stress as reflected in brain activity, such as increased amygdalar activity in response to pain and transmitter systems involved in the stress response [93, 96, 97].

All adverse events (AEs) and spontaneously reported reactions will be collected during each experimental session and for 7 days after each session. Commonly expected reactions that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe. Common, expected reactions are defined as those most frequently reported in the literature and include: anxiety, 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. Serious adverse events (SAEs), adverse events leading to subject withdrawal from the study, and changes to psychiatric status will be collected throughout the protocol. Medications used to treat the specified AEs will be collected during the study, and all changes to psychiatric medications will be collected throughout the study.

6.1.3 Process Measures

Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze audio/video data from selected preparatory, experimental and integrative sessions. Participants will be asked to read a brief script for a computer program that will enable transcription of audio recordings from these sessions. The elements included in adherence criteria are specific to each type of session. The goal of these ratings will be to correlate therapist adherence to the Treatment Manual with outcome as a part of the sponsor's ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.

Belief of condition assignment and certainty will be collected from each therapist responsible for treating the subject and the subject at the integrative session on the day after each blinded experimental session in Stage 1. At the primary endpoint, the Independent Rater for the study will also provide their guess and certainty of condition assignment prior to unblinding. These beliefs are collected as a part of the sponsor's ongoing initiative to optimize the triple-blind as a part of dose response studies.

Subject opinions about having three versus two experimental sessions will be collected from each subject at the Primary Endpoint after unblinding and the 2-month follow-up in Stage 1. Stage 2 subjects will complete the same measure at the Secondary Endpoint and the 2-month follow-up in Stage 2. These opinions (referred to as "perceptions" in the Time and Events Table) are collected as a part of the sponsor's ongoing initiative to assess the therapeutic value of the third experimental session and to gather information on the optimal therapeutic dose for MDMA.

The Reactions to Research Participation Questionnaire (RRPQ) [98] is an assessment of causes for taking part in research and responses to the experience of being a research subject. Subjects will complete this measure during their 2-month follow-up, with exact time of completion varying in accordance with participation in the third open label experimental session in Stage 1 or in Stage 2. The RRPQ is intended to assess the subject's experience as a research subject, perceived reasons for consenting to be a research subject and perceived freedom to take part in the study.

Table 3.Stage 1 Time&Events	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	Enrollment	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Primary Endpoint	Experimental Session 3	Integrative Sessions	End of Stage 1 & Outcome
Visit Timing or Study day or Window	Up to 2 months prior to Visit 1		Prior to V5 [M]	Up to 7 weeks post V1	Before V9 [A]	3-5 weeks post V5	Before V13 [A]	1 month post V9	3-5 weeks post V9 [N]	Before V18 [A, N]	May happen over > 1 day. 2 mo. post V14 [N]
Initial Phone Screen	X										
Informed Consent	X										
Medical/Psychiatric History	X										
General Phys. Exam (BP, Pulse, Temp)	X										
Brief Neurological Exam	X										
ECG	X										
SCID-I-RV	X										
Clinical Lab Tests, 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 [L]		X	X	X	X	X	X [L]	X	X	X [L]
General Well-Being		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 [B]							
CAPS, GAF, BDI-II, PTGI, PSQI, DES-II (IR)	X							X			X
NEO PI (Ind. Rater)	X							X			
C-SSRS		X	X	X [C, D, E]	X [I]	X [C, D, E]	X [I]	X	X [C, D, E]	X [I]	X
Administer IP Drug + Therapy, SOCQ				X		X			X		
Monitoring of BP, Pulse and Temp.				X		X			X		
SUD				X [F, E]		X [F, E]			X [F, E]		
Beliefs of Condition Assignment					X [K]		X [K]			X [K]	
Overnight Stay				X		X			X		
Integrative Therapy Session					X		X			X	
7 days Integrative Telephone Contact					X [I]		X [I]			X [I]	
AEs Requiring Medical Attention				X	X	X	X	X	X	X	X
Spont. Reported Reactions and all AEs				X	X	X	X		X	X	
Changes in Tinnitus and/or Pain	X [O]		X [E, O]	X [E, O]	X [E, O]	X [E, O]	X [E, O]	X [O]	X [E, O]	X [E, O]	X [O]
AEs of psychiatric status or withdrawal		X	X	X	X	X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X	X	X	X	X
Issue Memory Aid Card [H]											X
Unblinding [J]								X			
Perception of Third Session								X [N]			X [N]
RRPQ											X [H]

A =First Integrative session is 1 day after exp session B = At least 24 hrs prior to 1st exp. session C =Approximately 6 hours post MDMA D =At the beginning of the session E =As needed F=Approximately every 60 minutes G =Given on 2nd preparatory session after meds are tapered (V3) H = Only for subjects starting Long term Follow up and not going to Stage 2 I =For 7 days post Exp. Session, C-SSRS D2 and D7 of calls only, General well being for all 7 days J =Subjects in the medium or low dose group will not have visits 14-18, but will instead move onto Stage 2. K= On the day of the 1st integrative session following the Exp. Session L=CAPS may be videotaped M=First preparatory session (V2) may happen at the time of screening, before enrollment. N= Full dose subjects only. O= Only in subjects with pre-existing tinnitus and/or chronic pain.

Table4.Stage2Time&Events	Preparatory	Experimental Session 1		Experimental Session 2			Experimental Session 3		Follow-Up	Long Term Follow up after Stage 1 or Stage 2	Long Term Follow-Up
Visit #	V19*	V20	V 21,22,23	V24	V 25,26,27	V28	V29	V 30,31,32	V33		1 Year Follow-up
Type of Visit	Preparatory Session	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Secondary endpoint	Experimental Session 3	Integrative Sessions	End of Stage 2 & Outcome		Follow-Up & Outcome
Visit Timing or Study day or Window	Within maximum of 5 months of V13*	After V19	Before V24 [A]	3-5 weeks post V20	Before V28 [A]	1 month post V24, beforeV29	3-5 weeks post V24	Before V33 [A]	May happen over > 1 day 2 months post V29		May happen over > 1 day. One Year post 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		X
Record to Audio/Video	X	X	X	X	X	X[H]	X	X	X[H]		
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-II, PTGI, PSQI, DES-II (IR)	Use V13*					X			X		X
NEO PI with Ind. Rater	Use V13*								X		X
C-SSRS	X	X[C, D, E]	X[G]	X[C, D, E]	X[G]		X[C, D, E]	X[G]	X		X
Administer IP Drug + Therapy, SOCQ		X		X			X				
Monitoring of BP, Pulse and Temp.		X		X			X				
SUD		X[D, F]		X[D, F]			X[D, F]				
Overnight Stay		X		X			X				
Integrative Therapy Session			X		X			X			
7 days Integrative Telephone Contact			X[G]		X[G]			X[G]			
AEs Requiring Medical Attention	X	X	X	X	X	X	X	X	X		
Spont. Reported Reactions[G] and all AEs		X	X[G]	X	X[G]		X	X[G]			
Changes in Tinnitus and/or Pain		X[D, I]	X[D, I]	X[D, I]	X[D, I]	X[I]	X[D, I]	X[D, I]	X[I]		X[I]
AEs of psychiatric status or withdrawal	X	X	X	X	X	X	X	X	X		X
Serious Adverse Events	X	X	X	X	X	X	X	X	X		X
Perception of Third Session						X			X		
Complete Stage 2, go to 1yr F/U									X		
RRPQ									X		
Issue Memory Aid Card									X		
Follow-up Questionnaire											X
Termination Visit											X

* If Visit 19 is more then 8 weeks after V13 then the measures from V13 will need to be repeated prior to starting Stage 2 A =First session is 1 day after Exp session B =Approximately 6 hours post MDMA C =At the beginning of the session D =As needed E =Approximately every 60 minutes F = Given on 2nd integrative session only G = For 7 days post Exp. Session, C-SSRS D2 and D7 of calls only, General well being for all 7 days H=CAPS may be videotaped I= Only in subjects with pre-existing tinnitus and/or chronic pain.

6.2 Study Procedure, Visit Descriptions and Adherence
To ensure consistency of the manualized therapy, each type of visit described below must follow the Treatment Manual. Adherence to the manualized therapy will be reviewed by monitoring of data and or rating videos of these visits as part of the data review process. All criteria for a visit type should be completed as a part of the visit series, which may take place over more than one day.

6.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study, Visit 1)
All individuals who are prescreened, as defined in this section, should be assigned a screening number and recorded on the Subject Screening Log where information on the selection of potential subjects in the trial should be collected. Prospective participants will be prescreened by telephone according to an IRB-approved script to learn if they meet basic eligibility criteria.

After telephone screening is completed, each potential participant will be given the informed consent form (ICF). The screening number will be used on all subject records prior to enrollment, including the ICF. After signing the ICF, participants will provide a medical and psychological history through interview and will undergo a general physical examination, performed by a physician who is not the Clinical Investigator. 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), ECG, clinical laboratory assessments to determine study eligibility (see Section 10.0 for list of laboratory tests). Tinnitus and chronic pain symptom severity will be collected using a visual analog scale in subjects with a medical history of these conditions. In addition, Human Immunodeficiency Virus (HIV) and, if indicated, 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 as 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 and the drug screen 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.

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. To establish independent rater reliability, the investigators will have the option to video record the screening CAPS interview in as many instances as necessary. The C-SSRS will also be administered at

screening to assess suicide risk. Suicide risk will also be assessed via psychiatric interview. The Clinical 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-II, PTGI (in reference to time since the trauma), PSQI, DES-II and NEO-PI. The entire visit should take between 1.5 and 2.5 hours. Screening may take place over more than one day and up to four months prior to Visit 1 (enrollment). The participant may also have the first preparatory session (Visit 2) prior to enrollment.

If eligibility is confirmed, the participant will be enrolled and will be issued a subject number and contacted to schedule 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 (the last day the medication was taken) and the first experimental session being at least five times the drug and active metabolites' half-life, plus one week for stabilization. The first experimental session will be scheduled to occur after washout is complete, if applicable.

6.2.2 Preparatory Sessions (Visits 2-4)
The investigator will inquire about any possible changes in the participant's health to ensure that the subject continues to meet eligibility criteria and if applicable, will confirm that they have adhered to the schedule for tapering off medications. In subjects who have pre-existing tinnitus or chronic pain, the visual analog scale will be used to collect the severity of symptoms.

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.

Adherence criteria for preparatory sessions should be completed as a part of one of the three sessions. These elements do not have to be accomplished in any specific order or in every preparatory session. Generally, adherence criteria for these sessions include that the therapists will work with the subject to prepare for MDMA-assisted psychotherapy. The therapists and subject will seek to form a strong working relationship with each other, and they will help the subject prepare for upcoming experimental sessions. Preparatory sessions will promote a safe set and setting for confronting trauma-related memories, emotions, and thoughts, which is intended to develop therapeutic alliance.

The first preparatory session (Visit 2) may take place at the time of the screening and before enrollment. All eligible participants must be enrolled prior to the second preparatory session (Visit 3) and in maximum four months after the screening starts.

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 undergoing medication washout will repeat the C-SSRS at a point after washout is complete but before the first experimental session.

The attendant, described below, will remain with the participant during each overnight stay after each MDMA-assisted psychotherapy session. He or she 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 may 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.

Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol.

6.2.3 MDMA Sessions [Visits 5, 9, and 14 (Visit 14 for full dose group only)]
Subjects in Stage 1 will receive two experimental sessions of MDMA-assisted psychotherapy blinded with respect to dose, scheduled approximately 3-5 weeks apart. Subjects in the open label third experimental session in Stage 1 will receive experimental sessions with the full dose of MDMA.

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 low dose conditions.

Adherence criteria for experimental sessions should be completed as a part of each experimental session. These elements do not have to be accomplished in any specific order. Generally, adherence criteria for these sessions include that the therapists will

create and communicate a setting of safety and support the subject during periods of inner focus. Therapists will use a largely nondirective approach, following the lead of the subject's inner healing intelligence. Therapists will provide encouragement for staying present with difficult experiences. Therapists may occasionally offer gentle guidance or redirection as a choice to encourage collaborative exploration if the subject repeatedly avoids trauma related material. Therapists will inquire about somatic symptoms and if necessary encourage release of tension through movement, in whatever way feels appropriate to the subject. Therapists will use music to support the experience without being intrusive.

On the day of the MDMA session, the participant will arrive approximately one hour 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 Clinical 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 headphones 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 [99, 100]. They may also request periods of music if they wish. 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 [101]. 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 may 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. For subjects without a diagnosis of controlled hypertension, after viewing baseline values at the beginning of the session, the investigators will only view the blood pressure or pulse values in the case of a medical indication in order to improve the effectiveness of condition blinding. More frequent measures will be taken if the participant exhibits symptoms that could be related to hypertension, hypotension tachycardia or bradycarida. In the event of any medical indication, such as signs or symptoms that could be related to either hypertension or hypotension, the investigators have the option to print out the results during the session.

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 reactions during the session. If subjects who have pre-existing tinnitus or chronic pain mention any changes, the visual analog scale will be used to collect the changes in symptoms.

A supplemental dose half the size of the initial dose may be administered 1.5 to 2.5 hours after the initial dose upon mutual agreement between the investigators and the 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 has 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 complete the SOCQ after the end of the experimental session and prior to leaving the treatment facility the next day.

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 reactions, Adverse Events and Medications will be collected as described in Section 8 and 9 of the protocol.

6.2.4 Integrative Sessions 24 Hours after Experimental Session [Visits 6, 10, 15 (15 for full dose group only)]
On the morning after the MDMA session, the participant will meet with both investigators during a 90-minute integrative psychotherapy session.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or all in each and every integrative session. Generally, adherence criteria for these sessions include discussing material that emerged during experimental sessions and helping participants integrate their experiences both internally and into daily life. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone or pager. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

Participants will complete the C-SSRS during 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 reactions 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. If subjects who have pre-existing tinnitus or chronic pain mention any changes, the visual analog scale will be used to collect the changes in symptoms.

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 may 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.

Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol.

6.2.5 Daily Telephone Contact for Seven days after an Experimental Session
Investigators will follow the most recent version of the Treatment Manual in all matters relating to follow-up subsequent to the experimental psychotherapy sessions.
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. On the second and seventh day of telephone contact, the C-SSRS will be administered to monitor for suicide risk.

Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol.

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 needed. 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
In addition to the session the morning after each experimental session, the subject will have two additional integrative psychotherapy sessions with the therapists lasting 90 minutes between experimental sessions and in the month following the last experimental session in each stage. The therapists may conduct more sessions if they and the subject deem it necessary. (See Time and Events Table). 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. If subjects who have pre-existing tinnitus or chronic pain mention any changes, the visual analog scale will be used to collect the changes in symptoms.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or all in each and every integrative session. Generally, adherence criteria for these sessions include integration of material that emerged as a part of experimental sessions and afterward into daily life. Therapists will validate the choices of the subject to communicate or not on these thoughts, feelings and experiences. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone or pager. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

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 may 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 additional 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.

Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol.

If an integrative session falls within the seven-day period of telephone contact, it will replace the day of telephone contact, and spontaneously reported reactions will be recorded as reported during the session.

6.2.7 Evaluation at Primary Endpoint & Unblinding (Visit 13)

The primary endpoint evaluation in Stage 1 will occur one month after the second blinded experimental session. This visit will consist of two meetings that may be completed on separate days, one with the independent rater and the other with the therapists.
The blinded independent rater will administer: CAPS to assess PTSD symptoms, BDI-II to assess depression symptoms, GAF to assess general psychological function, PTGI to assess post-traumatic growth (in reference to start of the study), PSQI to assess sleep quality, DES-II to assess dissociation symptoms and NEO PI to assess personality. The blinded independent rater will provide their belief of the subject's condition assignment.

After completing all assessments and measures with the independent rater, the subject will meet with the therapists for approximately 30 minutes. Following the visit with the independent rater the blind will be broken for the subject's condition assignment. The independent rater will remain blind to condition assignment at this time. The therapists will assess suicidality with the C-SSRS. The visual analog scale will be used to collect

changes in subjects who have pre-existing tinnitus and chronic pain symptoms.

If the subject had been assigned to receive medium dose or low dose MDMA, the therapists will discuss continuation to Stage 2. Low and medium dose subjects will not complete the third experimental session and associated integrative sessions in Stage 1. Participants who decline continuing to Stage 2 will complete the Responses to Research Participation Questionnaire (RRPQ). If participants had been assigned to the full dose condition in Stage I, they will provide their perceptions of experimental sessions at this point. The therapists will discuss scheduling the third open label full dose experimental session and integrative sessions.

Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol.

6.2.8 Evaluation Two Months after the Third Experimental Session (Visit 18- Full dose subjects only, End of Stage 1)

The final evaluation for full dose subjects in Stage 1 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-II, PTGI (in reference to the start of the study), DES-II and the PSQI. The independent rater will assess participants on the GAF. Administration of CAPS may be recorded to video.

After completing all assessments and measures at the evaluation at the end of Stage 1 with the independent rater, the full dose subjects will meet with the investigators for approximately one hour. The investigators will administer the C-SSRS, and the subjects will indicate their perceptions of a third experimental session. Subjects will complete the RRPQ. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.

Subjects will receive a memory aid card for use between this visit and the 12-month follow up. Subjects will use this card to record AEs, medications and changes in psychiatric status that they will be asked about at the termination visit. Memory aids will not be collected. Subjects may return to taking psychiatric medications from this point onward if necessary.

6.2.9 Opportunity for Participants in Low Dose and Medium Dosage Condition to Enroll in Open-Label Study Segment ("Stage 2")

Low dose and medium dose participants who elect to enroll in Stage 2 will undergo a course of therapy and evaluation nearly identical to the full dose group in Stage 1, but given in an open-label context.

6.2.10 Open-Label Study Segment for Low Dose and Medium Dosage Participants (“Stage 2”)

Participants assigned to receive low dose or medium dose MDMA during Stage 1 will undergo three open-label MDMA-assisted psychotherapy sessions that follow a course and schedule similar to Stage 1 for the full dose group except that participants will

undergo one instead of three introductory sessions. After confirming consent and eligibility criteria, participants continuing to Stage 2 will meet with both investigators conducting psychotherapy for a single review and preparatory psychotherapy session before the first open-label MDMA-assisted psychotherapy session. If more than 8 weeks have passed since the primary endpoint, all measures will be repeated for a new baseline prior to the first open-label experimental session. Experimental sessions will be conducted according to procedures described in Section 6.2.3. During the first experimental session, subjects will receive a 100 mg initial dose of MDMA and may receive a 50mg optional supplemental dose of MDMA. At the beginning of each of the second and third experimental sessions, the co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg initial dose of MDMA. If a 100mg initial dose of MDMA is selected, an optional supplemental dose of 50mg MDMA may be administered. If a 125mg initial dose of MDMA is selected, an optional supplemental dose of 62.5mg MDMA may be administered. If the PI decides not to administer the optional supplemental dose and/or the optional clinical titration dose in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container in the safe.

Integrative sessions will be conducted according to procedures described in Sections 6.2.4 and 6.2.6. Phone calls will be conducted according to procedures described in Section 6.2.5.At the secondary endpoint based on procedures described in Section 6.2.7, the Independent Rater will administer the CAPS and GAF. Subjects will complete the BDI-II, PSQI, PTGI (in reference to the start of the study), and DES-II.Administration of the CAPS may be recorded to video.

Investigators will follow the most recent treatment manual in all matters relating to the Open-Label Stage 2 experimental psychotherapy sessions

Spontaneously reported reactions, SAEs, AEs and medications will be collected and reported in the same manner as during Stage 1. The visual analog scale will be used to collect changes in subjects who have pre-existing tinnitus and chronic pain symptoms as in Stage 1.

6.2.11 Assessment Two Months after Third Open-Label Session (End of Stage 2)

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, which may be recorded to video, and assess participants on the GAF, and participants will complete the BDI-II, PTGI (in reference to the start of the study), PSQI, DES-II, and NEO-PI. Participants will also complete C-SSRS and RRPQ with the therapists. Participants will provide their perception of the experimental sessions. Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.

Subjects will receive a memory aid card for use between this visit and the 12-month follow up. Subjects will use this card to record AEs, medications, and changes in psychiatric status that they will be asked about at the termination visit. Memory aids will not be collected. Subjects may return to taking psychiatric medications from this point onward if necessary.

6.2.12 Evaluation 12 Months after Final Experimental 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 assess participants on GAF, and participants will complete the PTGI (in reference to the start of the study), BDI-II, PSQI, DES-II and NEO PI. 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. A researcher who is a part of the study team may ask the subject questions about positive or negative effects about the study in person or on the phone 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. The visual analog scale will be used to collect changes in subjects who have pre-existing tinnitus and chronic pain symptoms. Subjects will complete the termination visit at this time.

Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol.

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.

If a subject develops any exclusion criteria that in the opinion of the Medical Monitor, affects the safety of the subject, including psychiatric diagnosis, pregnancy or excluded medications, the subject will discontinue treatment.

Subjects will be clinically monitored after discontinuation of treatment by at least one of the therapists. The cause of discontinuation will be recorded in the subject's source records and CRF. Whenever possible, the tests and evaluations listed for the primary endpoint and 12-Month Follow Up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the investigators, Medical Monitor and/or Sponsor.

Subjects who discontinue treatment prior to the primary endpoint will be replaced. Individuals who replace these subjects will be assigned the next available subject number.

Subjects who discontinue treatment after the primary endpoint in Stage 1 will not be replaced. If Stage 1 subjects discontinue treatment before the primary endpoint, the site should contact the randomization monitor for replacement instructions. If there is an emergency requiring knowledge of subject's condition assignment, the blind may be broken for an individual subject. The investigator will be provided with sealed emergency unblinding envelopes corresponding to each Enrollment Code. These sealed envelopes will be stored in a secure limited access area and should remain sealed if there are no emergency unblinding events during the study. The therapists, independent rater, and subject will remain blind to condition assignment until unblinding at the primary endpoint. Unblinding at the primary endpoint will be done using the web-based randomization program. Detailed instructions will be provided to the site in a separate document.

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 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 and 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 assess 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. Since psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable, and requires proper facilitation and support from the therapists. Discontinuing PTSD medications and the acute and sub-acute effects of MDMA-assisted psychotherapy can produce shifts in mood and activation, which may increase likelihood of suicidal ideation or behavior.

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

All psychotherapy sessions may 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. 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

Spontaneously reported reactions and common adverse effects of MDMA are modest and have generally not been associated with serious discomfort by volunteers in previous studies in non-psychiatric or psychiatric populations. Spontaneously reported reactions may include anxiety, reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common reactions include drowsiness, impaired judgment, headache, restlessness, nausea, parasthesias (odd somatic feelings, such as tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, nystagmus (eye-wiggling) and sensitivity to cold. 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. Other spontaneously reported reactions include increased private worries (rumination) and needing more sleep. Sub-acute effects are reported less often than acute effects. Other common reactions in preliminary data from the initial study of MDMA-assisted psychotherapy in people with PTSD include muscle tension in approximately 20% and gastrointestinal discomfort or diarrhea in

approximately 3.3% participants receiving MDMA. 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 [43, 60, 68]. Women may be more sensitive to these effects than men [62]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change [49].

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 of above 140/90 mmHg or higher, but none of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [68, 75]. Table 2 shows the degree of increase in vital-sign measurements in the investigators' recently completed clinical trial. No subjects in other clinical trials using MDMA have required any clinical interventions for elevated blood pressure, pulse or temperature, and all values returned to normal spontaneously.

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 Clinical Investigator who recently conducted a study of MDMA-assisted psychotherapy in 21 participants 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: Mean Increases in Vitals over Baseline and Range of Values 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 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 [61, 62, and see the IB]. At least some of the physiological or psychological reactions listed above are very likely to occur. Proper preparation and follow-up support will reduce the impact of acute or sub-acute 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 [62], and ambient temperature does not enhance or attenuate this slight elevation in humans [44]. 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 [102-104]. 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 (immunsuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings [105-107]. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [104, 108]. 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 [109, 110], 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 [110]. 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 [111]. 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 [112-114]. However, monkeys will “pay” higher prices in lever presses for psychostimulants than they will for MDMA [115, 116]. 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 [117, 118], though studies of non-representative samples have reported higher rates of dependence [119]. Most regular ecstasy users report taking ecstasy no more often than once a week [120]. 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, [62]. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions in conjunction with 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 Clinical Investigator and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

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 [121], 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 [122-124], 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 [125, 126]. 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 Clinical 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 [127-129], with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin [130]. Similar changes can be induced by methamphetamine and other psychostimulants [131-133]. Previous studies in nonhuman primates overestimated human-equivalent doses [134], and previous studies in rodents may also have overestimated human-equivalent doses [135]. 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 [112, 136-138]. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [139]. 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 [140]. 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 [141-143], but with estimated SERT sites returning to normal or increasing in numbers with period of abstinence. Likewise, studies have detected impaired memory and executive function in ecstasy users [140, 144, 145]. 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 [146-149], though other studies also reported that abstinence from ecstasy did not attenuate memory impairment in heavy users [143, 150].

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[151-154]. 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 [117, 118], and it appears that polydrug use may contribute to this association [151, 155]. 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 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 [156-159]. The team also performed studies expressly in heavy ecstasy users [160-163]. 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 [156, 157]. 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 [156]. 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 [156]. 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 [164]. 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, [165, 166]. A survey reported that in women interviewed on their drug use during pregnancy, there was a link between self-reported extent of prenatal MDMA exposure and delays in infant development at 12 months [167]. 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 Clinical 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 labetolol), injectable epinephrine and other pressor agents, and other standard emergency drugs and equipment will be available on-site as a means of treating any potential allergic reactions or other medical emergencies. In addition to drugs, the crash cart will contain a defibrillator (with rhythm monitoring capability), an oxygen tank, a suction device, a pulse oxometer, an IVAC pump and intubation equipment (including laryngoscope, and endotracheal tubes). As is now common practice in emergency departments, an automatic blood pressure cuff will be used in place of intraarterial blood pressure monitoring equipment. 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 Emergency Medical Services (EMS), at which time Advanced Cardiac Life Support (ACLS) procedures will be instituted. With these personnel and equipment, the researchers, in conjunction with EMS if necessary would be able to begin treatment in the office and then transport the participant by ambulance if hospital admission were required.

8.0 Adverse Events

An Adverse Event (AE) is defined as any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected adverse event is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event. All AEs will be monitored by the investigators until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the investigator and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:

- Mild: No limitation in normal daily activity
- Moderate: Some limitation in normal daily activity
- Severe: Unable to perform normal daily activity

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

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

2. Possibly Related

The administration of the investigational product and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the

investigational product.

3. Probably Related

Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

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

8.1 Common Expected Reactions
Commonly expected reactions that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe. Spontaneously reported reactions may include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common reactions include drowsiness, impaired judgment, headache, restlessness, nausea, parasthesias (odd somatic feelings, such as tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, nystagmus (eye-wiggling) and sensitivity to cold. 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. Other spontaneously reported reactions include increased private worries (rumination) and needing more sleep. Sub-acute effects are reported less often than acute effects. Other common reactions in preliminary data from the initial study of MDMA-assisted psychotherapy in people with PTSD include muscle tension in approximately 20% and gastrointestinal discomfort or diarrhea in approximately 3.3% participants receiving MDMA. Spontaneously reported reactions will be collected during the experimental session and during the seven days of telephone contact beginning the day after each experimental session.

8.2 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.

8.3 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 Monitor:
Julie Holland, M.D.
NYU School of Medicine
200 East 33rd Street, Suite 16H
New York, NY 10016
Cell number: 917-608-6200
Voice mail: 212-358-5808
Fax number: 212-679-2623
Email: jholland@inch.com

Study Monitor:
Berra Yazar-Klosinski, Ph.D.
Phone number: 831-429-6362 ext. 104
Fax number: 831-429-6370
Email: berra@maps.org

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

- All SAEs will be collected from enrollment through termination.
- All AEs and common expected reactions will be collected on the day of MDMA administration and for seven days after each experimental session.
- Events requiring medical attention will be collected from the first experimental session through the subject's final assessment at the end of Stage 1 or Stage 2 (as appropriate).

- Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any AE leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

A Memory aid card will be provided to the subject on the last visit prior to the 12 month follow up to record information on medications taken to treat SAEs, AEs leading to withdrawal and psychiatric AEs during the period between the end of Stage 1 or end of Stage 2 and the 12 month follow-up evaluation. The memory aid card will not be collected, but information from the card will be used to aid the subjects in providing information to the investigator. This information may be collected by phone.

9.0 Collection of Concomitant Medications and Tapering Instructions
All medications, over the counter (OTC) and prescription will be collected from screening through 7 days after the final experimental session. From 7 days after the final experimental session through study termination only medications taken to treat SAEs and psychiatric AEs will be collected.

Concomitant medications will be recorded during screening. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the experimental session to avoid the possibility of drug interactions (the interval will be at least 5 times the half-life of the particular drug or its active metabolites, plus one week for stabilization). If necessary, the investigators will make plans for tapering off and discontinuing any contraindicated medication upon enrollment, in consultation with the prescribing physician.

The investigators will request information about any changes in medication. 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 until after the end of Stage 1 or Stage 2, with the exception of gabapentin when prescribed for pain control or stimulants for ADHD taken at baseline provided that they are discontinued 5 half lives before each MDMA session and are not restarted until 10 days after each MDMA administration. The investigators may prescribe a designated rescue medication 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).

Subjects must be willing to refrain from taking any psychiatric medications during Stage 1 and Stage 2, with the exception of gabapentin when prescribed for pain control. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for 10 days after each experimental session.

Medication Tapering Table

Generic Name	Brand Name	Half-life (hours) including active metabolites	Days for Washout
alprazolam	Xanax	11	3
aripiprazole	Abilify	75	16
atomoxetine	Strattera	5-24	5
bupropion	Wellbutrin	21	5
citalopram	Celexa	35	8
clonazepam	Klonopin	30-40	8
diazepam	Valium	20-70	15
duloxetine	Cymbalta	12	3
escitalopram	Lexapro	32	7
fluoxetine	Prozac	7-9 (days)	45
imiprimine	Tofranil	6-18	4
lamotrigine	Lamictal	25	6
lorazepam	Ativan	12	3
mirtazapine	Remeron	20-40	8
olanzapine	Zyprexa	21-54	11
paroxetine	Paxil	21	5
prazosin	Minipress	2-3	1
quetiapine	Seroquel	6	2
risperidone	Risperdal	3-20	4
sertraline	Zoloft	26	6
temazepam	Restoril	8-12	3
trazodone	Desyrel	9	2
venlafaxine	Effexor	12	3
ziprazidone	Geodon	7	2
zolpidem	Ambien	2.5	<1

The CI may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual). Rescue medications may be a benzodiazepine, zolpidem or other anxiolytic or sedative according to the physician's clinical judgment. SSRIs, SNRIs, and MAOIs should not be used as rescue medications.

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

a. Subjects will refrain from taking any herbal supplement (except with prior approval of the research team).
b. Subjects 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 subjects 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 Clinical 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, if indicated, Hepatitis C serology will be performed.

A urine-dip pregnancy test for females of childbearing potential and a urinary drug screen 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 in order to comply with GCP guidelines and to ensure validity of the study data. From the start of the study, videos from selected sessions will be reviewed for adherence to the Treatment Manual and therapeutic alliance. Adherence will be checked by monitoring and by review of selected video data. 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 Good Clinical Practice (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 Sponsor will judge the clinical and statistical significance of the study and estimate effect size and statistical power based on a comparison of observer-blind data collected at baseline and the primary endpoint using the primary outcome measure, which is the CAPS.

The sample selection is expected to produce acceptably homogeneous groups due to their diagnosis of with PTSD with CAPS scores of at least 50 who have not responded to treatment. There is no expectation that conditions will differ significantly in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, as depression.

The sponsor will examine individual CAPS, BDI-II, PTGI, PSQI, DES-II and GAF scores at baseline and the primary endpoint, in low dose, medium dose and full dose conditions. Descriptive statistics will be calculated for all measurements overall and by condition. Distributional characteristics will be examined for outliers and extreme values and, if either is evident. If outliers are found in primary or secondary outcome measures, the sponsor will perform analyses with and without the outlying data. Effect sizes for all outcome measures for primary endpoint, Stage 1, secondary endpoint, end of Stage 2, and 12-month follow-up will be estimated using Cohen's techniques.

All analyses of data from the primary endpoint will contain blinded data. Analysis of variance will be used to compare Global CAPS scores by dose condition at the primary endpoint.

Analysis of variance, or nonparametric analysis if assumptions are not met, will be used to compare the dose conditions for change in BDI-II, PTGI, PSQI, GAF, DES-II and NEO PI scores separately. If scores cannot be examined sufficiently in this model, then analyses will compare available data through the use of difference scores.

The sponsor will examine open-label data collected two months after the third Stage 1 experimental session. The sponsor will perform a within-subject analysis of full dose participants.

Subjects who discontinue treatment prior to the primary endpoint will be asked to complete an outcome assessment prior to continuing to the long-term follow-up. The data from these subjects will be tested for equivalence to data from subjects completing the study per protocol. If found to be equivalent, data from these subjects will be presented as

an exploratory intent to treat analysis to examine results without bias towards subjects more likely to complete the study per protocol.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The sponsor will informally or formally compare peak blood pressure, heart rate and body temperature for participants after sessions after low, medium or full dose MDMA. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

The sponsor will collect Changes in Tinnitus and/or Pain visual analog scale scores from any subject reporting tinnitus or chronic pain during each point of administration, including baseline, experimental and integrative sessions, the primary endpoint, and two-month follow-up. The sponsor will plot and examine all Changes in Tinnitus and/or Pain visual analog scale scores across all three groups and within the dose groups for trends. Formal analysis of Changes in Tinnitus and/or Pain visual analog scale scores will only occur if three or more subjects complete Changes in Tinnitus and/or Pain visual analog scale at baseline and primary endpoint. Likewise, formal between-groups analyses will not be performed if all primary endpoint scores are from subjects assigned to the same condition. The sponsor will perform an independent t-test on the difference between baseline and primary endpoint Changes in Tinnitus and/or Pain visual analog scale scores in the full dose and comparator dose conditions, with p. set at 0.05. If the only scores available are for subjects in a single condition, then a paired t-test will be performed comparing baseline and primary endpoint Changes in Tinnitus and/or Pain visual analog scale scores, with p. set at 0.05.

Descriptive statistics will be computed for SOCQ scores completed after each MDMA-assisted psychotherapy session, and SOCQ scores will be compared across each of the three MDMA dose conditions and after full dose given during Stage 2. The data will be explored for effects of condition on responses to the SOCQ.

Descriptive statistics will be calculated for subject's perceptions of experimental sessions. Mean, standard deviation and range of individual responses will be examined. Perceptions of experimental sessions will be examined during Stage 1 and Stage 2, before and after participant have undergone a third experimental session and will be compared within subjects.

The sponsor will collect ratings of adherence to the treatment manual from specifically selected types of sessions. Descriptive statistics will be computed for each adherence scale within a given session. The sponsor will explore the factors and structure of the measures of adherence to assist in further development of adherence and competence measures. If sufficient data is available, the sponsor will correlate the mean adherence ratings for adherence scale and session type with Global CAPS scores to investigate the effects of adherence to the treatment manual on reduction in PTSD symptoms. If it is found that there are specific factors within the adherence scales, then the factor will be correlated with Global CAPS score.

Qualitative interviews conducted by a researcher who is part of the study team during the 12-month follow-up visit will be transcribed to text. A computer-assisted qualitative data analysis software package will be utilized to assist in thematic content analysis of the interview transcripts. A member of the research team will code the interviews for content, to identify emerging themes and organize data into thematic constructs utilizing a grounded theory approach. Descriptive statistics will be calculated for emerging themes.

There may be an interim analysis of the data that will not affect study conduct for safety and efficacy before all participants have completed the 12-month follow-up.

12.1 Statistical power

The literature does not provide an estimate of the effect size for change in CAPS after sessions using an low dose or medium -dose MDMA. The proposed study will provide these important estimates. With the current amendment, the sponsor is increasing the group size in each condition, and all subjects will complete the primary endpoint. This may increase statistical power in this study, and will provide important estimates of effect size that can be used to develop a dose response model.

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 the study must be given 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 ICF, 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, 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 that will be stored separately from other documents, all data will be identified only by the participant's initials on the source document and four-digit subject number. 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 Clinical 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 may 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. CAPS assessments may also be recorded to video to establish inter-rater reliability. Full names and addresses will not appear in these recordings.

Any use of recordings for purposes other than research or training (e.g. 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 by unauthorized persons. 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 or trainees greatly reduces the risk of a breach of confidentiality.

13.2 Costs to Participants
There will be no costs to the study participants for any study-related procedures. 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 Clinical 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. Some 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. These documents will be filed according to ICH-GCP regulations in the Investigator Site File (ISF). It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

15.0 Publication Policy

The sponsor recognizes the importance of communicating medical study data and therefore encourages publications in reputable scientific journals and presentations at seminars or conferences. It is understood by the PI that the information generated in this study will be used by the sponsor in connection with the development of the investigational product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the PI is obliged to provide the sponsor with complete test results, all study data, and access to all study records. It is mandatory that all data analysis is done on the official monitored sponsor database and that the analysis plan is agreed upon with the sponsor statistician.

Any results of medical investigations with the sponsor products and/or publications/ lectures/manuscripts based thereon, shall be exchanged and discussed by the PI and the sponsor clinical research representative(s) prior to submission for publication or

presentation. Due regard shall be given to the sponsor's legitimate interests, e.g. manuscript authorship, obtaining optimal patient protection, coordinating and maintaining submissions to health authorities, and coordinating with other studies in the same field.

The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Trial Agreement.

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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 [43], see also 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 [36, 38, 59, 168, 169]. There have been no unexpected drug-related SAEs during the course of a study of MDMA-assisted psychotherapy in people with PTSD under the direction of the Clinical 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 internal medicine as well as psychiatry and who maintains ACLS certification, and a psychiatric nurse or licensed therapist who will maintain Basic Life Support (BLS) certification. The Clinical Investigator and assisting investigator will thus provide a team that is prepared 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. 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 Clinical 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 Clinical 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 Clinical 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 C-SSRS. 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.

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. 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 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 ECG evidence of AMI [170].

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 non-hemorrhagic 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 [171, 172].

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 for psychotherapy sessions will be done with two cameras operated remotely by the investigators 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 secure locations. A third copy of video recording of any experimental or non-drug psychotherapy session can be made for any subject who requests it.

Participants will be asked to read a brief script for a computer program that will enable transcription of audio recordings. 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 secure location. 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 or analyze MDMA-assisted psychotherapy for sponsor-supported studies.

Recording to video of CAPS assessment by the independent rater will be done in the office of one of the raters.

Full names and addresses will not appear in video or audio recordings. 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.