

PROTOCOL MP-7

IND #63-384

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An Open-Label Lead-In and Randomized, Active Placebo-Controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Jordan

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1.0 List of Abbreviations

AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI	Beck Depression Inventory
C	Celsius
CAPS	Clinician Administered PTSD Scale
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPCL	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intra-venous
LSD	d-lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
NK	Natural Killer
PRN	As needed
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
RRPQ	Reactions to Research Participation Questionnaire

SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for Diagnoses
SERT	Serotonin Transporter
SL	Sublingual
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
US	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 US-based 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 (US) pilot study, IND #63-384 (MP1). MAPS is currently sponsoring other Phase 2 studies in Switzerland and Israel, with the Swiss study to be completed in about nine months and the Israeli study in about eighteen months. An additional Phase 2 study is planned in Canada.

This is the first study of the therapeutic potential of MDMA to be conducted in Jordan. It will take place in Amman, Jordan at the Al-Rashid Hospital. This study has been designed as part of an international, multi-site research program sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS; www.maps.org). MAPS' long-term goal is to develop MDMA into a prescription medication.

This Phase 2 study is a randomized, double-blind, partial crossover study with active placebo-controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in patients with treatment-resistant posttraumatic stress disorder (PTSD). An open-label lead-in will be conducted prior to beginning the randomized portion of the study. The lead-in portion of the study will enroll two subjects. Once the first subject has completed three experimental sessions and the second subject has completed two experimental sessions, an internal review of data will be completed. After review, an additional 10 subjects will be enrolled into the blinded portion of the study (Stage 1) for a total of 12 subjects. Subjects assigned active placebo may crossover to the open-label arm of the study (Stage 2) once they complete the blinded portion of the protocol.

The design of the lead-in, and Stage 2 open-label portions of the study will be identical. Subjects will receive a full dose of MDMA during each of three sessions scheduled one month (within a window of 3-5 weeks) apart, with psychotherapy sessions occurring before and after each day-long experimental (MDMA-assisted) psychotherapy session. These sessions will occur on a weekly basis, with the exception of psychotherapy sessions occurring on the morning of the day after each experimental session. In Stage 1 the randomized, active placebo-controlled, double-blind portion of the study, ten participants will be enrolled, with seven receiving the experimental full dose of MDMA and three receiving an "active placebo" dose of MDMA during three sessions scheduled approximately one month apart. Participants who receive an active placebo Stage 1 will have the opportunity to take part in Stage 2, a second phase of the study that follows the same procedures, but all subjects will receive the full dose of MDMA. In Stage 1 PTSD symptoms will be assessed at baseline and two months after the third experimental session, this will be repeated for subjects in Stage 2, two months after the third experimental session.

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

2.2 Protocol Purpose

2.3 Supporting Information:

2.3.1 Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder arising after a personally threatening life-event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. The DSM-IV (APA 1994) criteria for PTSD include:

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

PTSD is a worldwide public health problem for which a wider array of effective treatments is needed. The lifetime prevalence of PTSD in the US general population is between 6 and 10% [1], but it is common in other countries as well [2-6]. In US soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [7], and it is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [8]. In 2004 alone, the US Department of Veterans Affairs (VA) spent \$4.3 billion on PTSD disability payments to approximately 215,000 veterans, most of them from the Vietnam War [9]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [10-12].

The search for novel and more effective treatments is therefore of major public health and economic significance. PTSD is typically a chronic illness [13, 14] associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [4, 13, 15, 16]. People with PTSD face challenges in relationships and with work productivity [17]. In the US National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In both subgroups, more than one-third of the patients still had symptoms several times per week after 10 years [18]. The number of people who do not improve after treatment is between 40% and 60%. In a 2002 comparison of two types of psychotherapy for women with PTSD after sexual assault, 47% of each treatment group was diagnosed with PTSD based on high CAPS scores [19]. Another study reported similar figures [20].

Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [21]. An array of psychotherapeutic options currently exists for treating PTSD, and two selective serotonin reuptake inhibitors (SSRIs; sertraline and paroxetine) are currently approved as PTSD treatments in the US. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies or respond in a way that falls outside of clinical significance [22, 23]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [24]. These findings suggest that there is still a substantial need for innovative treatments for PTSD.

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

2.3.2 MDMA-Assisted Psychotherapy for PTSD

Both psychotherapy and pharmacotherapy are used in the treatment of PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proved to be effective in treating some symptoms of PTSD [28], although some patients may have to undergo more than one treatment to reduce or resolve those symptoms [20]. However, a recent meta-analysis concluded that all “bona fide” psychotherapies, including those listed above, are similarly effective with PTSD [29].

MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that may enhance or amplify certain aspects of psychotherapy. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients [30-33]. This form of treatment consists of several sessions of MDMA-assisted psychotherapy within the context of a brief to moderate (i.e., three- to four-month) course of non-drug psychotherapy. MDMA-assisted psychotherapy is hypothesized to reduce or ameliorate the hypervigilance, emotional numbing, and withdrawal expressed by individuals diagnosed with PTSD.

Anecdotal accounts, an uncontrolled clinical trial, and data from the recently completed clinical trial described above all suggest that MDMA may provide unique benefits to people with PTSD when administered in combination with psychotherapy [30-33]. It may assist people in confronting memories, thoughts, and feelings related to the initial trauma while diminishing the fears that sometimes arise in response to such confrontation. An increase in self-acceptance and increased feelings of closeness to others may also assist people with PTSD to develop a stronger and more productive relationship with their therapist.

Treatment goals include alleviating symptoms and correcting the stress-induced neurochemical abnormalities associated with the condition. One approach is to discover drugs

that directly counteract these neurochemical changes. Paroxetine and sertraline are the only two drugs approved in the US by the FDA for treating PTSD, and are known to affect the serotonergic components of PTSD. 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 individuals with PTSD [34]. Another approach to treatment is to develop drugs and/or psychotherapeutic treatments that will more indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal associated with PTSD.

Reports of past experience with MDMA-assisted psychotherapy suggest that it may also counteract the effects of PTSD. The biological and psychotherapeutic approaches overlap and reinforce each other. Knowledge about the connections between the neurobiological and the therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala [35]. 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 [36, 37].

2.4 Previous MDMA Research

To date, MDMA has been administered in Phase 1 and Phase 2 studies to approximately 440 subjects without any occurrences of drug-related serious adverse events (SAEs) [38-50].

The full initial and supplemental doses to be used in this study are identical to those in use in previous and ongoing studies taking place in the US, Switzerland, and Israel; and the lowest initial and supplemental doses are only slightly higher than active placebo doses in completed or ongoing research. Previous researchers have also used doses within this range [39, 46, 51-54]. Doses equal to or exceeding 125 mg have been used in previous uncontrolled and controlled studies of MDMA [39, 51, 55-58]. Prior to the time MDMA was placed in Schedule I, identical or similar doses and regimens were used in psychotherapy [31, 32, 59]. The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes 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.

We have chosen to use active placebo MDMA doses on the basis of their demonstrated ability to produce detectable subjective effects in the absence of fully therapeutic effects [53, 56]. The active placebo dose in this study is 15 mg greater than the active placebo dose used in previous studies, and is expected to produce slightly more detectable effects, thus making it a more effective placebo. The initial dose of 40 mg MDMA is not expected to produce a significant reduction in anxiety or a significant increase in access to emotionally upsetting material, though this dose may produce slight alterations in consciousness such as increased relaxation or tension [53]. The cumulative dose of 60 mg will be close to doses reported in street Ecstasy tablets [60]. It is possible that the combined dose will produce a greater number of drug effects, but because of the split dosage, they are not expected to produce the effects expected of a full 60 mg dose.

3.0 Protocol Objectives

The objective of this study is to explore the safety and efficacy of MDMA-assisted psychotherapy in patients with treatment-resistant PTSD. The study will examine participants receiving either a full experimental dose or an active placebo dose of MDMA. The study will also gather information from an open-label lead-in and in an open-label phase of the study for people who received the active placebo dose of MDMA during the randomized, double-blind, active-placebo controlled phase of the study.

3.1 Primary Objectives

- The protocol will assess changes in PTSD symptoms as measured via Clinician-Administered PTSD Scale (CAPS) score at baseline and two months after the third experimental session in the randomized “Stage 1” of the study. The protocol will also assess PTSD symptoms via CAPS in participants enrolled in the open-label “Stage 2” two months after the third open-label session.

3.2 Secondary Objectives

- The protocol will assess PTSD symptoms through CAPS, at baseline and two months after the third open-label session for participants in the open-label lead-in.
- The protocol will assess symptoms of depression with the Beck Depression Inventory (BDI) at baseline and two months after the third experimental session in the randomized “Stage 1” of the study. Likewise, the protocol will assess depression symptoms via BDI in participants enrolled in “Stage 2” two months after the third open-label session.

3.3 Safety Objective:

To monitor and assure safety during the full dose and active placebo doses of MDMA in participants throughout the clinical protocol through assessing physiological effects, spontaneously reported side effects and suicidality.

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) at baseline, during the second preparatory session, twice during each experimental session (approximately one hour before and five to six hours after drug administration), once during all integrative sessions following experimental sessions, on the second and seventh day of telephone contact after each of the three experimental sessions, and two months after the third experimental session. The same schedule of assessment will be employed during the open-label lead-in and during Stage 2.
- Quality of life, as assessed via Global Assessment of Functioning (GAF) will be made at the same point in time as CAPS is administered by the independent rater. Global functioning will be assessed at baseline and two months after the third experimental session for participants in the randomized study, and two months after a third open-label study for participants in the open-label lead-in and participants enrolled in Stage 2.

- SUDS and vital signs to include blood pressure, heart rate and temperature will be measured during each experimental session, and comparisons will be made for SUDS and vital signs during and after each experimental session and during and after placebo administration.
- Adverse events and side effects will be collected during and after each experimental session. All serious adverse events (SAEs) and adverse events of concern to the participant will be collected throughout the protocol.

4.0 Investigational Product

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 [59, 61]. In the first completed study of MDMA-assisted psychotherapy in people with PTSD, the principal investigator of this protocol reported reduction in PTSD symptoms, as assessed by an independent rater, in people who received MDMA with psychotherapy instead of placebo [62]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion [51, 53, 54, 58, 63-65]. Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with ecstasy (see for example [51] versus [66]). An increase in positive mood, increased access to emotionally intense material, increased interpersonal trust and compassion for the self and others, and anxiolysis likely all contribute to the therapeutic effects of MDMA. It is significant that anxiety is reduced without depressing the sensorium, and that patients can still experience and reflect upon intense emotions. Increased interpersonal closeness may permit patients to explore usually upsetting thoughts, memories or feelings. Facilitated recall and unusual and potentially innovative shifts in thinking and perception may contribute to generating new perspectives about past or current thoughts, feelings and experiences.

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 [67-69]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower.

4.3 MDMA Doses, Compounding, and Labeling

4.3.1 Doses:

The first two participants enrolled in the lead-in will be assigned to open-label treatment with the full experimental dose of 125 mg MDMA followed by an optional dose of 62.5 mg 1.5 to 2.5 hours later.

4.3.2 Compounding

After data from the lead-in subjects has been reviewed, ten subjects will be enrolled in the randomized blinded phase of the study Stage 1. Stage 1 is a randomized, double-blind, partial crossover design that includes an active placebo condition. Seven participants will receive the full experimental dose consisting of an initial dose of 125 mg of MDMA followed by an optional supplemental dose of 62.5 mg 1.5 to 2 hours later. Three participants will receive an active placebo with an initial dose of 40 mg MDMA followed by an optional supplemental 20 mg dose. After the follow-up two months after the third experimental sessions in Stage 1, participants who received the active placebo will have an option to receive the full 125 mg/62.5 mg dose in open-label MDMA-assisted psychotherapy sessions during Stage 2.

4.3.3 Compounding

MDMA in bulk will be sent to the investigator/pharmacy for compounding, and the pharmacy will provide inactive compound. MDMA will be weighed into capsules of 125, 62.5, 40 and 20 mg (calculated as the weight of the hydrochloride salt), with capsules for initial dose different in color from capsules for supplemental dose. Additional inactive material (lactose) will be used to ensure that active dose capsules are of equal weight to full-dose capsules. Compounding of the following conditions will be performed or observed by the individual with the appropriate license for handling regulated compounds.

- Experimental Session 1 dose 1 (125 or 40 mg)
- Experimental Session 1 dose 2 (62.5 or 20 mg)
- Experimental Session 2 dose 1 (125 or 40 mg)
- Experimental Session 2 dose 2 (62.5 or 20 mg)
- Experimental Session 3 dose 1 (125 or 40 mg)
- Experimental Session 3 Dose 2 (62.5 or 20 mg)

4.3.4 Labeling

The doses of MDMA for a single subject to complete three experimental sessions will be stored in a single box (see box label). Each dose of MDMA for each experimental session will be labeled and stored individually with in the box (see container labels for each session and dose). Labels will be provided by the sponsor.

Examples of Blinded Labels

Box Label
MAPS Study# <u>XXXX</u>
Investigational Product: MDMA
Dose: Blinded (125mg, 62.5mg OR 40mg, 20mg)
Randomization # <u>XXX</u>
Subject Number _____
Lot #: XXXXX
Administer as per protocol
Caution-Limited by Law to Investigational Use Only

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

Initial and supplemental doses for each of the three experimental or open-label sessions will be stored in seven separate containers, with each container holding a single capsule. Dose 1 will be 125 mg MDMA or 40 mg MDMA in combination with inactive compound to make capsule weights equivalent, and Dose 2 will be 62.5 mg MDMA or 20 mg MDMA combined with sufficient lactose to produce equivalent weights. Labels will include protocol number, drug name, lot number, dosage number, the sponsor name and a statement that the drug is for investigational use only. The doses for Stage 1 will be blinded Labels for all open-label sessions will receive identical labeling except that each label will state the dose 125mg or 62.5 mg MDMA.

4.4 MDMA Accountability

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

4.5 MDMA Storage and Handling

MDMA will be stored and handled in compliance with all relevant local and international regulations. MDMA is a Schedule 1 compound and will be stored and handled in compliance with relevant national regulations. In accordance with Jordan Food and Drug Administration requirements, the license-holder or licensed pharmacist will be responsible for storing and dispensing the MDMA. It will be stored in a secure safe within the hospital pharmacy used to store methadone and other strictly regulated compounds, in accordance with or approved by national drug authorities. Only the license holder will have access to the safe. The room in which the safe is mounted has an alarm system and will be locked whenever the investigator or his nurse is not present.

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

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant national regulations. They will be kept separate from other records and will be maintained in a locked cabinet mounted to the wall in a locked office with an alarm system.”

4.6 MDMA Stability

The product to be used in this study was synthesized by Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by Prof. Dr. R. Brenneisen, DCR, University of Bern, Switzerland. The same batch of MDMA has been used in sponsor-supported studies of MDMA-assisted psychotherapy in Switzerland and Israel and will be used in a similar study in Canada. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94. 1 B5.5 with no decomposition products detectable and a HPLC purity >98%.

5.0 Protocol Design

The randomized, double-blind, active-placebo controlled partial crossover study will examine the safety and efficacy of MDMA-assisted psychotherapy in patients diagnosed with treatment-resistant PTSD of at least six months duration. The open-label lead-in and Stage 1, the randomized, double-blind, active-placebo controlled phase of the study and Stage 2, the open-label phase will follow the same sequences of events. The schedule will include three separate day-long sessions of MDMA-assisted psychotherapy one month apart (with in a window of 3-5 weeks). The experimental sessions will be preceded by up to three introductory sessions and each experimental session will be followed by three or more integrative sessions. In Stage 1 and the open-label lead-in PTSD symptoms will be assessed at baseline and two months after the third experimental session. For subjects entering Stage 2, PTSD symptoms will also be assessed upon entry into Stage 2 and two months after the third experimental session in Stage 2.

The open-label lead-in will enroll two subjects. The blinded phase Stage 1 will proceed after the first open-label subject has completed 3 experimental sessions, the second subject has completed at least two sessions and data has been reviewed by MAPS to ensure proper therapist training and subject safety. Data review will consist of at least three of five transcripts of experimental sessions reviewed by MAPS, entry criteria, vital signs and side effect data for completed sessions and any other adverse events. In stage 1 subjects will be randomly assigned to receive three MDMA-assisted sessions with either an experimental full dose of 125 mg MDMA followed by an optional supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 40 mg MDMA followed by an

optional dose of 20 mg MDMA 2.5 h later. Those participants who receive the active placebo dose will be offered an option to enroll in the open-label "Stage 2" of the protocol unless at this point they meet any exclusion criteria for Stage 2 participation.

MDMA will be administered in the context of three separate day-long psychotherapy sessions by a male/female co-therapist team. The second and third sessions will be scheduled approximately one month from a prior session. Each of these sessions will be followed by an overnight stay at the clinic, an integrative psychotherapy session the next day, and daily telephone calls for the next seven days

An independent rater will assess PTSD symptoms with the CAPS and symptoms of depression with the BDI. The rater will assess participant quality of life with the GAF. Baseline assessments of symptoms of PTSD and depression and quality of life ratings will be compared with assessments made two months after the third double-blind session in Stage 1. The blind will be broken for all participants in Stage 1 after completing this assessment. Participants in the active placebo condition will have the opportunity to enroll in Stage 2, the open-label phase of the study. Stage 2 consists of three open-label sessions of full dose MDMA-assisted psychotherapy. The independent rater will assess PTSD symptoms two months after the third open-label session.

5.1 Planned Duration of Protocol

The open-label lead-in and the randomized, double-blind, active placebo controlled study segment will both last approximately four and a half months from screening and baseline evaluation up until the evaluation two months after the third experimental session. The study will last an additional four months for participants who go on to the open-label Stage 2, for a total of about 8 months. If the investigators enroll two participants every month, the entire study will be completed in a year and a half.

5.2 Randomization and Subject Numbering

Two participants will be enrolled in the open-label lead-in study, and assigned to the full-dose condition. Ten participants will be enrolled in the randomized study. A blinded randomization will be used for this study in order to maintain a 7/3 ratio between participants in the Full Dose and Active Placebo conditions. An individual working with the sponsor will generate a list of randomized numbers, and a local (on-site) randomization monitor will be in charge of randomization. Randomization will be performed within the 24 hour period before the first experimental session. Subjects will be assigned in a blinded fashion to the next available randomization number on the list upon enrollment in the study. The randomization numbers will be pre-printed on the drug packaging labels.

Participants who replace any participant who has withdrawn from or been removed from the study will be assigned the next consecutive number in the series. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant. For this purpose, the randomization monitor will provide the investigators with a numbered sealed envelope corresponding to each container with an enclosed card indicating the condition order for that container. These sealed envelopes will be stored in the safe and

opened only in the event that early unblinding is required. In all other cases, the blind will be maintained until all participants have completed the study. The investigators and participant will be blind to condition (sequence of administration) assignment.

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 five-digit subject number. The first two digits will always be "07" and will identify the study site. The next three digits identify the subject within the site and will be assigned sequentially, with 001 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 07001, second 07002, etc.

Participants in the open-label lead-in and stage 2 open-label section will all be assigned to the experimental dose condition, and the participant, the investigators and the rater will be aware of condition assignment.

5.3 Recruitment and Subject Population

Candidates for participation will be twelve patients diagnosed with PTSD of at least six months duration that has not responded to prior treatment. Participants must be at least 18 years old with a diagnosis of PTSD and a Clinician Administered PTSD Scale (CAPS) score equal to or greater than 50 at baseline evaluation. Candidates for study participation will be recruited from patients of the investigators and colleagues, by letters of referral sent to other psychiatrists and psychotherapists and through word of mouth. All recruitment materials and advertisements will be approved by the institution's IRB/EC.

5.3.1 Inclusion Criteria

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

1. Meet DSM IV criteria for current PTSD of at least six months duration.
2. Have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
3. Have had unsuccessful treatment (defined as still meeting PTSD criteria post-treatment) with one of the following:
 - a. Treatment with a selective serotonin uptake inhibitor (SSRI), mirtazapine or a monoamine oxidase inhibitor (MAOI)
 - b. Any form of psychotherapy for the treatment of PTSD.
4. Are at least 18 years old
5. Are willing to commit to medication dosing, experimental sessions, and follow-up sessions and to complete evaluation instruments.
6. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. An exception to this may arise in the case of designated rescue medication that may be administered in the event of a crisis during or after the experimental session.
7. Agree not to change the type or frequency of current psychotherapy, nor change therapists until after the third experimental session (if they are concurrently seeing an outside therapist)
8. Agree to, for one week preceding each MDMA/placebo session:
 - a. Refrain from taking any herbal supplement (except with prior approval of the research team)

- b. Refrain from taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
 - c. Not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team) Note: Must have physician's approval.
9. Agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.
10. Are willing to remain overnight at the study site after each experimental session until the non-drug session occurring the next morning.
11. Are willing to be driven home the morning after the experimental sessions, after the non-drug therapy session either by a driver arranged by the subject or by the site personnel or taxi.
12. Are willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
13. (If female participants of childbearing potential), must be willing to have pregnancy tests and must agree to use an effective form of birth control.
14. Are literate. They must be proficient in reading documents written in Arabic, and they must be able to effectively communicate with the therapists and other site personnel.

5.3.2 Exclusion Criteria

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

1. Are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control, including sexual abstinence.
2. Have a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.
3. Diagnosed with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
4. Have evidence or history of significant (controlled or uncontrolled) hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).
5. Have hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
6. Weigh less than 48 kg.
7. Have used "Ecstasy" (illicit drug preparations purported to contain MDMA) more than 5 times or at any time within the previous 6 months.
8. Would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
9. Require ongoing concomitant therapy with a psychotropic drug.

10. Meet DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.
11. Are not able to give adequate informed consent.
12. Have any current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol.

6.0 Methods

After consenting to take part in the protocol, participants will be screened by site personnel who will obtain medical and psychological history by interview and perform a general physical examination, brief neurological exam and clinical laboratory assessments. Participants will also undergo the SCID and assessment via Clinician-Administered PTSD Scale (CAPS) for psychiatric diagnosis and to determine participant eligibility. If, after reviewing all information, the investigators conclude that a participant is eligible, they will arrange and schedule at least one introductory session with the investigators.

If tapering medication is necessary, the first experimental session will be scheduled to occur after washout is complete. After undergoing three 60 to 90 minute introductory psychotherapy sessions with a male/female co-therapist team, the two lead-in study participants will undergo the first of three approximately eight-hour long experimental sessions with full-dose MDMA, and the ten subjects in the randomized portion of the study will randomly receive either the experimental or active placebo dose of MDMA. Each experimental session will be scheduled approximately three to five weeks apart. Participants will undergo one non-drug-psychotherapy session approximately 24 h after the start of each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. PTSD symptoms will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions. The rater will assess PTSD symptoms once prior to MDMA-assisted psychotherapy, once approximately two months after the third experimental session in Stage 1, and two months after the third open-label session in Stage 2. The independent rater will assess the participant on the GAF, a scale where clinician observation is used to assess global quality of life and psychological function, at the same time points listed above. Participants will complete the BDI, a self-report measure of symptoms of depression, at baseline and two months after the third experimental session. All psychotherapy sessions, including MDMA-assisted sessions, will be recorded to audio and video, with all recordings preserved for research purposes, and participants may receive any session recordings upon request.

Safety measures, vital signs and a measure of psychological distress will be administered during each experimental session, and a measure of suicidality will be administered at baseline, before and after each experimental session, during each integrative session following an experimental session, on telephone calls 2 and 7 days after each experimental session, and two months after the third experimental session. Participants will rate their current degree of subjective distress with a single-item, self-report scale, the Subjective Units of Distress (SUD) scale, repeatedly during the MDMA session, with the degree of distress marked along seven points.

6.1 Assessments and Measures

6.1.1 Outcome Measures

The primary outcome measure will be the Clinician-Administered PTSD Scale (CAPS), a clinician-scored measure for PTSD diagnosis and measure of symptom intensity and severity. The CAPS provides a means to evaluate the frequency and intensity dimensions of each symptom, impact of symptoms on the patient's social and occupational functioning, overall severity of the symptom complex and global improvement since baseline and the validity of the ratings obtained. The CAPS takes approximately one hour to complete. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [70, 71]. An independent rater will assess all participants at study baseline and two months after the third experimental session. The same independent rater will assess all participants enrolled in stage 2 two months after their third open-label session.

The Beck Depression Inventory (BDI) is a 21-item a self-report measure of depressive symptoms [72, 73] that will serve as a measure of depression. It takes five to ten minutes to complete. An Arabic translation of the measure exists [74]. Participants will complete the BDI at the same times when the CAPS is administered.

The Reactions to Research Participation Questionnaire (RRPQ) [75] is an assessment of causes for taking part in research and responses to the experience of being a research participant. Participants will complete this measure during their final study visit, with exact time of completion varying in accordance with participant enrollment in the open-label study segment or in the fourth open-label MDMA-assisted psychotherapy session. The RRPQ is intended to assess the participant's experience as a research subject, perceived reasons for consenting to be a research participant and perceived freedom to take part in the study, and is not an outcome measure.

The Global Assessment of Function (GAF) is a measure of quality of life and general function made through observations. The GAF consists of a single score, with scores ranging from 0 to 100, with 100 reflecting superior function and zero reflecting serious risk of causing harm to the self or others. The independent rater will assess all lead-in and randomized study participants at baseline and two months after the third experimental or open-label session. Participants enrolled in Stage 2 will be assessed on the GAF two months after the third open-label Stage 2 session.

6.1.2 Safety Measures

Safety measures, vital signs and a measurement of psychological distress will be assessed during both experimental sessions. Participants will rate their current degree of subjective distress with a single-item, self-report scale, the Subjective Units of Distress (SUD) scale, repeatedly during both experimental sessions, with the degree of distress marked along seven points.

Participants will rate their current degree of subjective distress with a single-item, self-report scale, the Subjective Units of Distress (SUD) scale, repeatedly during the MDMA session, with the degree of distress marked along seven points.

The C-SSRS (Arabic translation) is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [76]. It consists of a "Baseline" form that assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions, and can be administered during face to face interview or over the telephone. The C-SSRS will be administered 24 times during the open-label lead-in and randomized study; at baseline, after the second preparatory session, twice during each experimental session (once just prior to drug administration and once five to six hours after drug administration), after each integrative session, on the first and last days of daily telephone contact occurring after the integrative session after an experimental session, and on the visit which takes place approximately two months after the third experimental session. Participants undergoing medication washout will complete the C-SSRS once prior to and once after medication washout, using the times above if possible but with additional measures used if none of the scheduled times occur just prior to or after medication washout.

Blood pressure and heart rate (as pulse) will be assessed periodically during each experimental session. Blood pressure and pulse will be measured at the outset of the experimental session, and once every half hour (0.5 hour, 30 minutes) duration of the study. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic or pulse 110 are exceeded. The investigators will measure participant body temperature via tympanic thermometer every 60 to 90 minutes. Cardiovascular effects will be assessed via blood pressure measurement (such as with an automatic inflating cuff). Body temperature will be assessed via tympanic thermometer.

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

Visit #	Pre-Study	V1	V 2,3,4	V5	V 6,7,8	V9	V 10,11,12	V13	V 14,15,16	V17
Type of Visit	Screening may take place over more than one day	Baseline	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Experimental Session 3	Integrative Sessions	Follow-Up
Visit Timing or Study day or Window	Up to 1 month prior to Visit 1	Day 1	Approx 1 week apart	3-4 weeks post baseline	Approx. 1 week apart	3-5 weeks post V5	Approx. 1 week apart	3-5 weeks post V9	Approx. 1 week apart	May happen over more than 1 day. 2 months post V 13
Informed Consent	X									
Medical/Psychiatric History	X									
General Physical Exam (BP, Pulse, Temp, brief systems check)	X									
Brief Neurological Exam	X									
ECG	X									
SCID	X									
Clinical Lab Tests, w/ HIV test	X									
Collect Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Medication Taper (if applicable)	X	X								
Study Enrollment after meeting I/E		X								
Record to Audio/Video			X	X	X	X	X	X	X	
General Well-Being		X	X	X	X	X	X	X	X	X
Drug Screen	X			X		X		X		
Pregnancy Screen (if applicable)	X			X		X		X		
Complete Randomization Procedure				X ^G						
CAPS and GAF	X	X								X
BDI	X									X
C-SSRS		X	X ^E	X ^{A, B, C}	X	X ^{A, B, C}	X	X ^{A, B, C}	X	X
Administer IP Drug+Therapy				X		X				
Monitoring of BP, Pulse and Temp.				X						
SUDS				X ^{B, D}		X ^{B, D}		X ^{B, D}		
Beliefs of Condition Assignment				X		X		X		
Overnight Stay				X		X		X		
Integrative Therapy Session					X		X		X	
RRPQ										X ^F
7 days Integrative Telephone Contact					X		X		X	
Adverse Events Requiring Dr. Visit			X	X	X	X	X	X	X	X
Spontaneously Reported Side Effects				X	X	X	X	X	X	
Adverse Events of Concern			X	X	X	X	X	X	X	
Serious Adverse Events		X	X	X	X	X	X	X	X	X
Study Termination/ Unblinding										X

^A Approximately 6 hours post MDMA ^B at the beginning of the session ^C as needed ^D Approximately every 60 minutes ^E Given on second preparatory session only ^F Stage 1 only; Stage 2 at end of Stage 2 ^G = Within 24 hours prior to first experimental session

6.2 Visit Descriptions

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

Once participant gives written informed consent, a screening number will be assigned. The screening number will be used on all subject records prior to enrollment. Participants will provide a medical and psychological history through interview and will undergo a general physical examination performed by a physician. The examination will involve the following procedures: blood pressure, pulse, height, weight, body temperature, examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities, brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function), electrocardiogram (ECG) serum electrolytes, metabolic profile, urinalysis and complete blood count. In addition, Human Immunodeficiency Virus (HIV) serology will be performed. Results of HIV serology will be kept confidential, and appropriate referral for counseling will be made if necessary. The clinical laboratory values will not be captured in the Case Report Form (CRF), but will be used to establish eligibility and will be kept with the subject's source record. A urine-dip pregnancy test for females of childbearing potential will be performed as well. If, upon examination, there are questions raised about possible medical problems, the investigators will request a review of participant medical records and request additional tests or assessments as indicated.

An independent rater who will not be present during any of the therapy sessions will administer the CAPS and assess the participant on the GAF. The C-SSRS will also be administered at screening to assess suicide risk. The participant will complete the BDI.

The investigator will perform the Structured Clinical Interview for Diagnoses to assess study eligibility.

After eligibility is confirmed the participant will be considered enrolled and will be issued a subject number. The investigators will review this information and will contact the participant if all inclusion criteria and no exclusion criteria are met and will schedule one or more preparatory sessions and, if possible, the first experimental session. Any participant who must refrain from taking a medication will begin tapering off that medication, with the first experimental session scheduled to occur after complete washout. The entire visit should take between one and a half and two and a half hours. This screening may take place over more than one day and up to one month prior to visit 1. Participants who require medication washout will be assessed on CAPS and GAF after medication washout, and the investigators will perform the C-SSRS once after medication washout but prior to the first experimental session. This may occur during a scheduled administration of the C-SSRS during the second preparatory session, or at an additional time appropriate to the medication washout.

6.2.2 Preparatory Sessions (Visits 2-4)

The investigator will inquire about any possible changes in the participant's health to

ensure that subject continues to meet eligibility criteria and if applicable, will confirm that they have appropriately tapered off of medications.

The participant will undergo three sixty to ninety minute introductory sessions with the therapist-investigators, who will be a male and a female therapist. The investigators will work with the participant to prepare him or her for MDMA-assisted psychotherapy. The investigators and participant will seek to form a strong working relationship with each other, and they will help the participant prepare for upcoming experimental sessions. Introductory sessions will promote a safe space for confronting trauma-related memories, emotions and thoughts. The participant and investigators will discuss goals for the MDMA session and will review what will happen during the MDMA session, following standard procedures and techniques discussed in the sponsor-developed treatment manual. The investigators will work with the participant to prepare him or her for MDMA-assisted psychotherapy.

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.

The investigators will introduce the participant to the attendant during one of the preparatory sessions. The attendant, described below, will remain with the participant during each overnight stay after each MDMA-assisted psychotherapy session. He or she will be an individual with previous training in managing psychological distress and will be the same sex as the participant. 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.

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

Introductory sessions will be recorded to audio and video, and participants can receive copies of one or more introductory sessions upon request. All SAEs will be recorded from the time the participant is enrolled at Visit 1.

6.2.3 Experimental Sessions (Visits 5, 9, and 13)

All participants in Stage 1 receive three double-blind experimental sessions of MDMA-assisted psychotherapy scheduled 1 month (three to five weeks) apart, and participants in the open-label lead-in and open-label Stage 2 will receive three sessions with the full dose of MDMA. Participants assigned to Full Dose will receive 125 mg MDMA possibly

followed by 62.5 mg MDMA during all experimental sessions, and participants assigned to Active Placebo condition will receive 40 mg possibly followed by 20 mg MDMA during all experimental sessions. The second session will be scheduled three to five weeks after the first experimental session, and the third session will be scheduled three to five weeks after the second session. Each experimental session will last approximately eight hours and include an overnight stay at the study site. Experimental sessions will be conducted by the male and female therapist. 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 and active placebo dose conditions. Participants in the open-label lead-in and open-label Stage 2 will receive three sessions that employ the experimental dose of MDMA.

On the day of the experimental session, the participant will arrive approximately one to one and a half hours prior to drug administration. Continuing eligibility will be confirmed and a urine drug screening and, if the subject is a woman of child-bearing potential, a urine pregnancy test will be performed. 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, and 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 investigators will review procedures for the MDMA session with the participant. The investigators will record the entire session to video and audio. Participants may receive a copy of audio or video recordings of their experimental sessions upon request. The session will last for approximately eight hours or longer, followed by an overnight stay at the study site.

Before administering MDMA, 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 SUDS just prior to initial dose administration.

The participant will complete the C-SSRS approximately one hour to a half hour prior to drug administration.

At approximately 10:00 A.M., participants will receive the initial dose of MDMA along with a glass of water. The participant will sit or recline on comfortable furnishings, and there will be eyeshades and a program of music available if the participant wishes to use them. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material [77-79]. The therapist-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. Water and electrolyte containing fluids will be available throughout the session within the limits described in Appendix A. Food will be available during the

latter part of the session. All experimental sessions will be recorded to audio and video in their entirety. 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 therapist-investigators will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapist-investigators will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging.

Blood pressure and pulse will be measured at the outset of the experimental session, and approximately every 30 minutes for the duration of the experimental session. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic or pulse 110 are exceeded. Participant body temperature will be measured via tympanic thermometer and participants will complete the SUDS every 60 to 90 minutes, until the session is over, allowing a window of up to 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the investigators can make a greater number of measurements as their clinical judgment dictates. The investigators will record any spontaneously reported side effects during the session. If the investigators conclude that it is appropriate to do so, they will initiate the first question of the C-SSRS at any point in the session if the participant is experiencing significant psychological distress that does not respond readily to processing with the therapists according to the methods described in the MDMA-assisted psychotherapy treatment manual.

Table 3. Schedule of procedures and measures for experimental sessions. All times are approximate.

TIME	Procedure or Action
9:00	Urine drug screen and pregnancy test. Participant acclimated to environment
9:45	Baseline BP, Pulse, Subjective Units of Distress Rating (SUDS)
9:55	2 nd Baseline BP, Pulse, BT, SUDS
10:00	Drug Administration , begin recording to audio and video
10:30	BP, Pulse.
11:00	BP, Pulse, SUDS, BT
11:30	BP, Pulse; Can administer supplemental dose
12:00	BP, Pulse, BT
12:30	BP, Pulse, SUDS
13:00	BP, Pulse
13:30	BP, Pulse, BT
14:00	BP, Pulse, SUDS
Every hour, and as needed	BP, Pulse,
Every 60-90 minutes	SUDS, Temp

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

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

A support-individual who has previously agreed to remain with the participant during the MDMA session may arrive during the session if the therapists agree.

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 video when they have established that the participant returned to baseline function or is very close to doing so.

If all medical parameters are acceptable and the subject is alert, ambulatory and emotionally stable, the session will end. The investigators will depart the site when they have concluded that the participant is emotionally and medically stable. During the experimental session and for one week after, site personnel will remain available to participants via 24-hour cellular phone.

Participants will be instructed not to use caffeine or nicotine for 6 hours after the dose of MDMA. Spontaneously reported side effects, AEs of concern to the participant, and AEs requiring a doctor's visit will be collected starting on the day of the MDMA session through the seventh telephone daily telephone call. All SAEs will be recorded. Participants will remain overnight in an appropriately furnished room at the study site. With the approval of the therapists, a significant other may accompany the participant during the overnight stay. A same-sex attendant will check in periodically on the participant during the overnight stay, even if a significant other is present. The attendant will monitor participant health and will help participants relax during the overnight stay. The attendant will be an individual with some previous training in managing psychological distress. 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 receive information that will allow them to contact the investigators during the overnight stay in the case of an emergency or request for additional support. 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.

6.2.4 Integrative Sessions 24 Hours after Experimental Session (Visits 6, 10, 14)

On the morning after each experimental session, the participant will meet with both investigators during a 90-minute integrative therapy session. Participants will complete the C-SSRS just prior to beginning each integrative session. Prior to integrative psychotherapy, the participant and both therapist-investigators will indicate their beliefs concerning participant condition assignment. During the integrative session, the participant and investigator will discuss and review events, thoughts, feelings and

memories that occurred during the experimental session. If necessary, the therapist-investigators will help the participant to reduce any residual psychological distress he or she is experiencing. The therapists will also encourage the transfer of states of acceptance, feelings of intimacy, closeness and reduced fear experienced in MDMA sessions to emotionally threatening everyday situations. The investigators will be supportive, validating the MDMA experience and facilitating understanding and emotional clearing. Therapists are accessible any time the participant needs support outside the scheduled integration sessions. The investigators will assess participant mental health and the presence of any remaining side effects during integrative psychotherapy immediately after each experimental session. Integrative psychotherapy sessions can also serve as an opportunity for the therapist-investigators to gather information about the effects of MDMA on the participant in an unstructured manner. After this psychotherapy session, a person previously selected will provide a ride home. If the participant is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the participant due to unforeseen events, the investigators will assist the participant in finding an alternative means of returning home. The entire integrative psychotherapy session will be recorded to audio and video. Participants may receive copies of this session upon request.

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

6.2.5 Daily Integrative Telephone Contact for Seven days after an Experimental Session

Starting on the day of the non-drug integrative psychotherapy session following each experimental session, one of the investigators will contact the participant via telephone on a daily basis for one week. The integrative 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 and to assess participant well-being. Additional telephone contact can be initiated at the request of the investigators or participant. Spontaneously-reported side effects, AEs of concern to the participant, AEs requiring a doctor's visit and concomitant medications for treatment of AEs will be collected. All SAEs will be recorded. On the second and seventh day contact after the experimental session, the participant will complete the C-SRRS over the telephone.

6.2.6 Integrative (Non-Drug) Psychotherapy Between Experimental Sessions (Visits 7-8, 11-12, 15-16)

The participant will have three 60 to 90-minute non-drug psychotherapy sessions with both therapist-investigators during the interval between the first and second experimental session, three more integrative sessions between the second and third experimental sessions, and three more integrative sessions after the third experimental session. The investigators may conduct more sessions if they and the participant deem it necessary. The participant and investigators will continue to work on supporting the participant as she or he considers his or her experiences during one or both experimental sessions. The investigators will use clinical judgment to assess the participant's psychological well-

being during this period of time. If there are any indications of continuing anxiety or distress, the investigators may arrange to work on reducing the distress at a specially scheduled non-drug therapy session, through continuing 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. Each integrative session will be recorded to audio and video, and participants may receive a copy of one or more integrative sessions upon request.

The C-SSRS will be administered just prior to beginning each integrative session. All SAEs, AEs of concern to the participant, and AEs requiring a doctor's visit will be collected through the follow-up phase of stage 1 and, if applicable, continuing through Stage 2. If an integrative session falls within the period of telephone contact and additional phone call is not required that day, all things normally collected during the telephone call will be completed in person.

6.2.7 Evaluation Two Months after the Third Experimental Session

The final evaluation in the double-blind portion of the study will occur two months after the third experimental session. Participants will meet the independent rater for 90 to 120 minutes. The independent rater will administer CAPS to assess PTSD symptoms, and assess participant psychological function and quality of life with the GAF. The participant will complete the BDI. The investigators will administer the C-SSRS to assess suicidality. All SAEs, AEs of concern to the participant, and AEs requiring a doctor's visit will be collected.

6.2.8 Unblinding and Enrollment into Stage 2 for Subjects in Active Placebo

After completing all assessments and measures at two months after the third experimental session in Stage 1, the participant will meet with the investigators for approximately one half hour, and the blind will be broken for each individual. All participants not continuing on to Stage 2 will complete the Responses to Research Participation Questionnaire and study termination. Participants who are not enrolled in Stage 2 may return to taking psychiatric medications. The independent rater will remain blind to condition assignment at this time.

The investigators will provide consent materials for Stage 2 to all participants in the active placebo condition

6.2.9 Open-Label Study Phase for Active Placebo Participants ("Stage 2")

A new informed consent will be signed by subjects before enrolling in Stage 2. Participants who elect to enroll in stage 2 will undergo the same course of therapy and evaluation as in Stage 1, but with full-dose MDMA during the 3 experimental sessions.

Assessment of PTSD symptoms two months after the third experimental session in Stage 1 will serve as baseline assessments in Stage 2. If the start of Stage 2 is delayed for more than 30 days from the time of the last CAPS in Stage 1 the independent rater will re-administer the CAPS and GAF and these scores will be used as the baseline for comparison to assessment after final open-label session in Stage 2.

After giving written informed consent, participants enrolled in Stage 2 will meet with both therapist-investigators for a single review and re-introductory psychotherapy session, followed by an open-label MDMA-assisted therapy session. Participants will have the same sequence of integrative therapy and open-label sessions scheduled approximately one month (three to five weeks) apart. The same safety measures will be administered during Stage 2, including C-SSRS before, during and after each open-label session, vital signs and subjective units of distress during each open-label session. Spontaneously reported side effects, AEs and SAEs will be collected and reported in the same manner as during the randomized study segment.

6.2.10 Assessment Two Months after Third Open-Label Session

All participants in the lead-in and in Stage 2 will be assessed by the independent rater two months after their final open-label session. The independent rater will assess all participants on the CAPS and GAF. Subjects will complete the RRPQ at the termination visit. Participants may return to taking psychiatric medications. All SAEs will be recorded.

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 experimental sessions and related visits that are critical for safety. If the investigator withdraws a participant from the session, the investigators will explain the reason for withdrawing the participant.

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

6.4 Premature Discontinuation of the Study

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

7.0 Risks Of Study Participation

7.1 Screening

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.

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

7.2 Risks and Discomforts Associated with Drawing Blood

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

7.3 Risks and Discomforts of Completing Assessments and Measures

Some measures contain items that may provoke negative emotions. It is possible that completing these measures could be upsetting.

7.4 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, experimental and open-label sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention (MDMA-assisted psychotherapy), and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

All psychotherapy sessions will be recorded to audio and video. Participants may feel uncomfortable with having their sessions recorded. The recordings will be used for developing a manualized form of MDMA-assisted psychotherapy, and participants may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment. Participants will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by investigators or regulatory agencies.

7.5 Risks of Receiving MDMA

Side effects of MDMA are modest and have generally not been associated with serious discomfort by volunteers in previous studies in non-psychiatric populations. Common side effects include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common side effects include restlessness, paresthesias (odd somatic feelings, such as tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, and

nystagmus (eye-wiggling). These effects are transient and wane as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects are reported less often than acute effects. More information on drug side-effects is contained in the Investigator's Brochure.

MDMA may produce mild alterations in sensory perception and altered perception of time [38, 51, 66]. Women may be more sensitive to these effects [54]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change [44].

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

7.5.1 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. Approximately 5% of participants enrolled in controlled trials with MDMA have had elevations in blood pressure above 200/100 mmHg or above a cut-off of 140/90 mmHg [57, 66]. Table 2 shows the degree of increase in vital-sign measurements in the investigators' recently completed clinical trial. No subjects in the completed trial or other clinical trials using MDMA have required any clinical interventions for elevated blood pressure, pulse or temperature, and all values returned to normal spontaneously. While maximum peak blood pressure during a given session in some cases rose above the cut-off for making more frequent measures (150 Systolic Blood Pressure (SBP) or 110 Diastolic Blood Pressure (DBP)). The degree of additional blood pressure and pulse elevation after a second dose of MDMA that is half the original dose and given 1.5 to 2.5 hours after the first dose is minimal. Preliminary data gathered by Michael Mithoefer, the principal investigator who completed a study in 2008 of MDMA-assisted psychotherapy in 21 participants with PTSD, reports that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose. The active placebo dose of MDMA may produce a slight elevation in blood pressure and heart rate [53].

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

All Experimental Sessions

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

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

7.5.2 Psychological Distress

Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following an MDMA session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from investigator, with occasional use of benzodiazepines for anxiety. In the proposed study, participants will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. 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 [53, 54, and see the IB]. At least some of the physiological or psychological side effects listed above are very likely to occur. Proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects, so that they will not be unduly troubled by them.

7.5.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [54], and ambient temperature does not enhance or attenuate this slight elevation in humans. Maximum body temperature could rise above normal temperature, as with the maximum peak of 37.78 ° C during the first experimental session in the sponsor's recent Phase 2 trial (n = 23, including all 21 participants and two drop-outs enrolled in this session, 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.

7.5.4 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 [80-82]. 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- γ and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings [83-85]. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [82, 86]. 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 [87, 88], 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 [88]. 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 is classified as a Schedule 1 compound, 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 reserved for drugs with high abuse potential and no known medical use [89]. 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 [90-92]. However, monkeys will "pay" higher prices in lever presses for psychostimulants than they will for MDMA [93, 94]. 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 [95, 96], though studies of non-representative samples have reported higher rates of dependence [97]. Most regular ecstasy users report taking ecstasy no more often than once a week [98]. Taken together, an examination of findings in humans and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants, Liechti and colleagues stated that “none of the participants expressed any interest in taking MDMA as a recreational drug” after receiving MDMA in a controlled research setting, (p. 166) [54]. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions and memories related to the original traumatic incident in addition to or even instead of increased positive mood or euphoria. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings. Mithoefer reported that few participants in the study of MDMA-assisted psychotherapy in people with PTSD reported desiring to take MDMA in an unsupervised setting.

In the currently proposed protocol, diversion is not an issue because MDMA will only be administered under the supervision of the principal investigator and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

7.5.6 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 [99], 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 [60, 100, 101], 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 [102, 103]. In the proposed clinical protocol, volunteers will be excluded on the basis of any conditions that might increase risk of adverse events occurring and participants will be carefully monitored for signs and symptoms of these unlikely events. Contingency plans for responding to these events are described in Appendix A.

7.5.7 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 [104-106], with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin [107]. Similar changes can be induced by methamphetamine and other psychostimulants [108-110]. Previous studies in nonhuman primates overestimated human-equivalent doses [111], and previous studies in rodents may also have overestimated human-equivalent doses [112]. 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 [90, 113-115]. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [116]. 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 [117]. 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 [118-120], but with estimated SERT sites returning to normal or numbers inversely related to period of abstinence. Likewise, studies have detected impaired memory and executive function in ecstasy users [117, 121, 122]. 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 [123-126], though other studies also reported that abstinence from ecstasy did not attenuate memory impairment in heavy users [120, 127]. 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 [128-131]. 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 [95, 96], and it appears that polydrug use may contribute to this association [128, 131-133]. Findings from retrospective studies are of limited value in estimating the potential risk of neurotoxicity from two doses of MDMA, as average cumulative dose and frequency of use in most of these studies is considerably higher than doses in human trials of MDMA. A better estimate of the potential risk of neurotoxicity can be found in findings from prospective studies comparing people before and after their first use of ecstasy.

Starting in the early 2000s, a team of researchers in the Netherlands has examined samples of people before and after reporting their first uses of ecstasy. These researchers have assessed estimated SERT sites, chemical markers of neuronal injury, changes in cerebral blood flow, performance and brain activity related to a working memory task,

and cognitive function in samples of ecstasy users reporting an average use of 1 to 3 tablets [134-137]. The team also performed studies expressly in heavy ecstasy users [138-141]. 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 [134, 135]. They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else [135]. Low use of ecstasy also failed to alter brain activity or performance on a measure of working memory [134]. When comparing cognitive function in people before and after their first use an average of 3.2 tablets and non-user controls at similar points in time, ecstasy users showed less improvement on a memory task than non-users [137]. 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 at least women who decided to use ecstasy had higher impulsivity scores prior to use [142]. 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 the MDMA-assisted session.

7.5.8 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 [143, 144], as discussed in the Investigator's Brochure. 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 for the duration of the study.

7.5 Medical Emergencies

The study site will contain equipment for assessing blood pressure, pulse and body temperature and there will be an automatic external defibrillator (AED) on site. The investigator or a member of the Al-Rashid Hospital staff will maintain basic life support (BLS) certification or its equivalent in Jordan in cardiopulmonary resuscitation (CPR) including training in using an AED. Similar arrangements are in use in completed or ongoing sponsor-supported research into MDMA-assisted psychotherapy. For a recently completed Phase 2 trial, the researchers have established (in communication with the U.S. 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 these personnel and

equipment, the researchers would be able to stabilize a participant in the office and then transport them to the ICU at the Al-Rashid Hospital.

8.0 Adverse Events

8.1 Adverse Events

Adverse Event (AE) - 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 trainee/subject's pre-existing condition.

2. Possibly Related

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

3. Probably Related

Exposure to the investigational product and AE are reasonably related in time and the

investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

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

8.2 Common Expected Side Effects

Commonly expected side effects that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe. Common, expected side effects are defined as those most frequently reported in the literature and include: Anxiety, Diarrhea, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Impaired Gait/Balance, Increased Irritability, Rumination (increased private worries), Insomnia, Jaw Clenching, Tight Jaw, Lack of Appetite, Low Mood, Muscle Tension, Nausea, Nystagmus, Parasthesias, Perspiration, Restlessness, Sensitivity to Cold, Thirst and Weakness. Spontaneously collected side effects will be collected during the seven days of telephone contact following an experimental session and the integrative session that occurs on the day after each experimental session.

8.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes 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 an on study SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not

result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

8.4 Adverse Event Collection

All SAEs will be collected for the duration of the protocol. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours of the investigator's awareness of their occurrence. All SAE reports should be faxed to ClinquestJo. A dedicated fax number will be provided to the site in the separate site specific instruction for SAE reporting. In addition to the fax, the PI should call ClinquestJo during normal working hours and verbally inform the CRO of the SAE. During off hours or if medical advice is needed immediately please call the sponsor Medical Monitor. An SAE reporting instruction with all contact numbers will be provided to the site prior to study start. All SAE faxes will go to ClinquestJo and will be reviewed by the CRO and sent to the sponsor.

Medical Monitor:

Michael C Mithoefer
[REDACTED]
[REDACTED]
[REDACTED]

Study Monitor:

Contracted CRO:
ClinquestJo
[REDACTED]

A dedicated fax and further instruction for SAE reporting will be supplied in the site-specific instructions. During off-work hours, reports can be faxed to the sponsor office at [REDACTED]. The CRO will review all adverse events.

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

- All SAEs
- Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions from MDMA administration through 7 days after the MDMA administration
- Any event of concern to the participant throughout the protocol
- Any adverse event leading to withdrawal from the protocol
- Common expected side effects will be collected on the day of MDMA administration and for seven days after each experimental session

9.0 Collection of Concomitant Medications and Tapering Instructions

Participant concomitant medications will be recorded during screening. If subject is being treated with psychoactive drugs at the time he or she is recruited into the study, the

prospective participant will be encouraged to discuss medication withdrawal with his or her outside treating physician, if any, and will be required to give the investigators permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA/placebo session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life).

The investigators will request information about any changes in medication just prior to each experimental session. Medications taken during the course of the protocol, including medications taken to treat AEs will be recorded either on a non-psychotropic or psychotropic concomitant medications CRF. Participants must be willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. Participants may receive a designated rescue medication that may be administered in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual). Participants must agree that, for one week preceding the MDMA session:

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

10.0 Clinical Laboratory Assessments

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

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

Serum electrolytes and the metabolic profile, which includes:

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

creatinine, serum;
globulin, total;
glucose, serum;
potassium, serum;
protein, total, serum;
sodium, serum;

CBC, which includes:

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

Urinalysis, which includes:

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

Thyroid function, which includes:

TSH high sensitivity;
Free T4;
Free T3.

In addition, HIV serology will be performed.

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

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

Clinical Laboratory

[REDACTED]
[REDACTED]
[REDACTED]

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

11.0 Study Monitoring, Auditing and Documentation

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

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

During or after the clinical protocol, Jordanian regulatory authorities, the U.S. FDA, the IRB, and/or representatives of the sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

12.0 Data Analysis

The investigators will examine data from the ten participants enrolled in the randomized study segment. They will examine the effects of active placebo versus experimental dose MDMA-assisted psychotherapy on symptoms of PTSD as assessed via CAPS global scores by conducting between subjects / within-subjects analyses of variance (ANOVAs) with condition (active placebo versus experimental) as a between-subjects variable and time of administration (baseline versus two months after third experimental session) as a repeated measure. The investigators will perform post-hoc tests on any interaction and probability of rejecting the null hypothesis will be set at 0.05. If there is a significant interaction between condition and time of administration, the investigators will perform separate between-subjects / within-subjects ANOVAs on CAPS sub-scale scores to examine whether any facet of PTSD symptoms is particularly affected by MDMA-assisted psychotherapy.

The investigators will examine the effects of active placebo versus experimental dose MDMA-assisted psychotherapy on symptoms of depression and quality of life through performing between subjects / within-subjects ANOVAS on BDI and GAF scores, with condition as a between-subjects variable and time of administration (baseline versus two

months after third experimental session) as a repeated measure with probability of rejecting the null hypothesis set at 0.05, and performing post-hoc tests upon any interactions.

The investigators may also perform a comparison of baseline and two-month follow-up CAPS, GAF and BDI scores that will include scores from participants in the randomized study and the open-label lead-in.

There will not be a sufficient number of participants enrolled in Stage 2 for formal analysis. However, the investigators will make observations and informal examinations of the effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression and quality of life before and after enrolling in Stage 2.

The investigators will maintain data for assessment of safety, including C-SSRS scores at each time point, assessment of blood pressure, psychological distress, and AEs. Safety analyses will examine data from open-label lead-in and randomized study subjects; if there are no significant differences in measures of safety for open-label lead-in and randomized study participants, then the investigators will combine safety data from both groups. They will collect data for blood pressure, pulse, body temperature and SUDS pre-drug administration baseline, approximately three hours after initial dose administration, seven hours after initial dose administration and peak values on case report forms. The investigators will compute descriptive statistics for these variables. Though formal analyses will not be possible for participants in Stage 2, descriptive statistics for all safety measures will be collected for Stage 2 participants.

12.1 Statistical power

The proposed study is a pilot investigation intended to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with PTSD. Because of their exploratory nature, pilot studies are often underpowered for detecting the desired effect. Because it is a pilot study in a small sample, statistical power is difficult to assess but it is likely to be low. The effect size reported for the initial study of MDMA-assisted psychotherapy in 21 participants with PTSD was calculated to be 1.1 (Mithoefer et al. Unpublished). The sponsor intends to conduct meta-analyses of CAPS scores gathered across all pilot-studies in addition to analyses of individual study data. Meta-analyses will be able to increase overall statistical power.

The sponsor used Java applications created by Lenth and posted on the website listed below to calculate estimated statistical power for this study, assuming an effect size of 0.6 for the impact of three sessions of MDMA-assisted psychotherapy on symptoms of PTSD and depression [145]. We initially conducted a two-sample independent t-test comparing one group of seven and another of three with effect size set at 1.1 and with equal sigma (estimated standard deviation) assumed and set at 1. The software calculated an estimated power of 0.2901, indicating an underpowered study.

13.0 Informed Consent

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

Information about events during the MDMA session must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of evaluation, preparatory, MDMA and integrative psychotherapy sessions, the information should include that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the MDMA session and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the investigator.

The investigator will provide a copy of the signed ICF to the subject, and will maintain the original in the investigator's study file.

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

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

13.1 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants in their role as research participants. Despite this, privacy cannot be guaranteed. Data collected from each participant will be identified only by the participant's initials on the source document and by a subject number. All measures, records, audio and video recordings will be kept in a locked file drawer in a locked office. Access to measures will be limited to regulatory agencies, researchers assessing the participant for changes in symptoms, sponsor representatives, and individuals analyzing data. Researchers with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Participants will sign forms for the release of information to any of the individuals who will need to obtain this information. Interested parties might include the prescribing physician or psychiatrist.

Participants will sign forms for the release of information, such as prior medical records, upon consent to permit screening for protocol enrollment. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data.

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

13.2 Costs to Participants

The sponsor of this study (MAPS) will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions, for the psychological and laboratory testing, for medical examinations, and for the study drug. The participant, their private medical insurance (if any), and the public health insurance plan will not be charged for any procedures done solely for the purpose of the study.

The participant or their private insurance remains responsible for on-going treatment unrelated to the study. MAPS will not cover medical expenses related to injuries which occur during the study period, but which are not directly related to study procedures.

13.3 Treatment and Compensation of Study Related Injury

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

14.0 Record Retention

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

15.0 Signature Page

Study title: An Open-Label Lead-In and Randomized, Active Placebo-Controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Jordan

Protocol: MP-7

I have read the foregoing protocol and agree to conduct the protocol as outlined. I agree to conduct the protocol in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

Investigator Signature

Date

Print name: _____

On behalf of MAPS, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this clinical protocol.

Sponsor Medical Monitor Signature

Date

Print name: _____

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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 [9], see also Section 6 of the “Investigator’s Brochure.” Psychiatrists in the US 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 [47, 125-128]. There have been no drug-related SAEs during the course of a study of MDMA-assisted psychotherapy in people with PTSD under the direction of the principal investigator for the proposed protocol. Procedures for monitoring for toxicity and risks for the training program will be similar to those employed in the study of MDMA-assisted psychotherapy in people with PTSD.

Although serious untoward reactions are unlikely, the researchers will closely and continuously monitor participants during the MDMA session. Throughout all sessions, participants will be attended by the investigators, a psychiatrist who is board-certified in emergency medicine and internal medicine as well as psychiatry and who maintains Advanced Cardiac Life Support certification, and a psychiatric nurse with experience working on a cardiac care unit before going into psychiatric nursing. The principal investigator and assisting investigator will thus provide a team of an experienced emergency physician and a registered nurse to respond in the unlikely event of a medical emergency.

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 by excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders), by preparing people before the experimental session, by creating an atmosphere of trust during the experimental session, by close monitoring, by daily contact with subjects for the period of a week after the

experimental session, and by providing non-drug integrative psychotherapy sessions. Subjects will remain in the offices of the principal investigator for the evening and night of each experimental session. The study site will be staffed by a trained attendant to respond to the needs of the subject. 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.

People diagnosed with bipolar affective disorder – 1 or with psychotic disorders will not be enrolled in the proposed study.

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.

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 him or her gain cognitive perspective of their experiences, and will help them implement the self-soothing and stress inoculation techniques presented during the introductory session. If this situation should occur during an integrative therapy session, at least one of the investigators will be available to stay with the participant for at least two additional hours.

- If a participant remains severely anxious, agitated or in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period the principal investigator will decide between one of two options:

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

- B. Hospitalization for stabilization.

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

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

In the event of a participant's experiencing severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an MDMA session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." This medication will be captured on a psychotropic concomitant medications CRF page. If a participant should become psychotic or suicidal, arrangements will be made for him or her to be admitted to the nearest inpatient psychiatric facility of their choice. 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 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. Treatment and response to potential AMI will follow the local guidelines and practices of Al-Rashid Hospital, Amman, Jordan. Following stabilization in the intensive care unit of Al-Rashid Hospital the participant will be transferred to a coronary care unit in a general hospital. Care will follow national and international guidelines and recommendations for treatment of potential AMI.

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 intensive care unit at Al-Rashid Hospital and prepared for transfer to a general for a head CT scan and further management in a specialized neurology unit and permitting time to administer recombinant tissue plasminogen if within three hours if needed. Treatment will follow national and international guidelines and recommendations for treatment of stroke.

Hyponatremia

History of hyponatremia or detection of hyponatremia on initial physical examination will be cause for exclusion from the proposed protocol. Participants will be given primarily electrolyte solutions, such as so-called or sports drinks, 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 Al Rashid hospital intensive care unit, 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 Al Rashid hospital intensive care unit.

Appendix B: Audio and Video Recording

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

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

Audio recording of experimental and non-drug psychotherapy sessions will be done using a laptop computer controlled by one of the investigators, with control allowing him to stop or start recording. The recordings will be written on an external hard drive connected to the laptop, not onto the laptop hard drive itself. The external hard drive will be kept in a locked office. The recordings will then be burned onto CDs in the investigators office. One copy will be stored by the investigators in a locked cabinet, another copy will be sent to the sponsor if requested and will also be stored in a locked cabinet at the location of the sponsor. An additional audio recording can be made of any psychotherapy session. The purpose of this is to enable the participants to have a recording for themselves at the end of each experimental session, rather than having to wait until the CDs are made by the investigators.