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-II	Beck Depression Inventory II
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
ESR	Erythrocyte Sedimentation Rate
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
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IV	intra-venous
JFDA	Jordanian Food and Drug Administration
LSD	d-lysergic acid diethylamide
MAOI	Monoamine oxidase inhibitor
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
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
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-methylenedioxymethamine (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 planning and/or sponsoring other Phase 2 studies in Switzerland, Israel, Canada and Spain.

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 subjects 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 to active placebo may crossover to the open label arm of the study (Stage 2) once they complete the blinded portion of the protocol. Subjects will be assessed twelve months after completing their final experimental session in Stage 1 or Stage 2.

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 apart (within a window of 3-5 weeks), 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 the randomized, active placebo-controlled, double blind portion of the study (Stage I), ten subjects 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. Subjects who receive an active placebo in Stage 1 will have the opportunity to take part in Stage 2, a second phase of the study that follows the same procedures, but with all subjects receiving 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 traumatic life event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. The DSM-IV (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 subjects 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 2002, a comparison of two types of psychotherapy for women with PTSD after sexual assault showed that 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 485 subjects without any occurrences of drug-related serious adverse events (SAEs) [38-55].

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 [45, 51, 56-59]. Doses equal to or exceeding 125 mg have been used in previous uncontrolled and controlled studies of MDMA [45, 56, 60-63]. Prior to the time MDMA was placed in Schedule I, identical or similar doses and regimens were used in psychotherapy [31, 32, 64]. The initial dose is expected to produce all the common effects of MDMA, including changes in mood, cognition and 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.

An active placebo MDMA dose was chosen on the basis of the demonstrated ability to produce detectable subjective effects in the absence of fully therapeutic effects [58, 61]. 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, so that the blinding is more effective for this study. 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 [58]. The cumulative dose of 60 mg will be close to doses reported in street Ecstasy tablets [65]. 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 subjects with treatment-resistant PTSD. The study will examine subjects receiving either a full dose or an active placebo dose of MDMA in the randomized, double

blind Stage 1. The study will also gather information from an open label lead-in and in the open label Stage 2 for subjects who received the active placebo dose of MDMA during Stage 1. Outcome measures will be administered by a blinded Independent Rater.

3.1 Primary Objectives

- The protocol will assess changes in PTSD symptoms as measured via Clinician-Administered PTSD Scale (CAPS) score at baseline and the end of Stage 1.

3.2 Secondary Objectives

- The protocol will assess PTSD symptoms via CAPS at the beginning and end of Stage 2.
- The protocol will assess PTSD symptoms via CAPS at baseline and the end of the open label lead-in.
- The protocol will assess symptoms of depression with the Beck Depression Inventory-II (BDI-II) at baseline and the end of Stage 1. Likewise, the protocol will assess depression symptoms via BDI-II at the end of Stage 2 and the open label lead-in.
- Quality of life, as assessed via Global Assessment of Functioning (GAF), will be completed at the same time as the other outcome measures. Global functioning will be assessed at baseline and the end of Stage 1, the open label lead-in and Stage 2 (if applicable).
- The protocol will assess PTSD, quality of life and depression symptoms at the long term follow up one year after the end of Stage 1 for each subject who received the full dose or who did not enroll in Stage 2. Likewise, each subject enrolled in Stage 2 will be assessed one year after the end of Stage 2.

3.3 Safety Objective:

The safety objectives of this protocol are to monitor and assure safety during the full dose and active placebo doses of MDMA in subjects throughout the clinical protocol by assessing physiological effects, spontaneously reported side effects and suicidality.

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during visits prior to experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition.
- SUD and vital signs to include blood pressure, heart rate and temperature will be measured during each experimental session, and will be compared between groups during and after each experimental session.
- Serious adverse events, adverse events and spontaneously reported adverse events ("side effects") will be collected during the study according to Section 8.

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 [64, 66]. In the first completed study of MDMA-assisted psychotherapy in people with PTSD, the principal investigator reported reduction in PTSD symptoms, as assessed by an independent rater, in people who received MDMA with psychotherapy instead of placebo [67]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion [56, 58, 59, 63, 68-70]. Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with ecstasy (see for example [56] versus [71]). 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 subjects can still experience and reflect upon intense emotions. Increased interpersonal closeness may permit subjects 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 [72-74]. 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 subjects enrolled in the lead-in will receive open label treatment with the full dose of 125 mg MDMA followed by an optional dose of 62.5 mg 1.5 to 2.5 hours later.

After the sponsor has reviewed data from the lead-in subjects, 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 subjects will receive the full 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 subjects will receive an active placebo with an initial dose of 40 mg MDMA followed by an optional supplemental 20 mg dose. After the evaluation at the end of Stage 1, subjects who received the active placebo will have the option to receive the full 125 mg dose followed by the optional supplemental dose of 62.5 mg in open label MDMA-assisted psychotherapy sessions during Stage 2.

4.3.2 Compounding

MDMA in bulk will be sent to the 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. Additional inactive material (lactose or similar material) 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)

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

Container label	Container label	Container label	Container label
MAPS Study # XXX Experimental Session #1 Dose 1 Randomization # XXX Subject #_____ Administer as per protocol Investigational Use Only	MAPS Study # XXX Experimental Session #1 Dose 2 Randomization # XXX Subject #_____ Administer as per protocol Investigational Use Only	MAPS Study # XXX Experimental Session #2 Dose 1 Randomization # XXX Subject #_____ Administer as per protocol Investigational Use Only	MAPS Study # XXX Experimental Session #2 Dose 2 Randomization # XXX Subject #_____ Administer as per protocol Investigational Use Only
Container label	Container label		
MAPS Study # XXX Experimental Session #3 Dose 1 Randomization # XXX Subject #_____ Administer as per protocol Investigational Use Only	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 eight 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 have blinded labels. 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 is a Schedule 1 compound in the U.S. and will be stored and handled in compliance with all relevant local and international regulations. In accordance with Jordan Food and Drug Administration requirements, the pharmacist will be responsible for storing and dispensing the MDMA. MDMA and records pertaining to its use will be stored in a secure location within the hospital pharmacy used to store strictly regulated compounds, in accordance with national drug regulations.

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.

4.6 MDMA Stability
The product to be used in this study was synthesized by Lipomed AG, Switzerland, in December 1998 (batch Nr. 94.1B5.51) with a purity of 99.66% analyzed by Lipomed on November 5, 1999. MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, 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. On February 26, 2010, a new quality control analysis was performed by Prof. Dr. R. Brenneisen, DCR, University of Bern, Switzerland. This analysis reconfirmed identity, purity and content of MDMA HCI Lipomed Batch no.94. 1 B5.5 with no decomposition products detectable and a HPLC purity of 99.9%.

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 subjects diagnosed with treatment-resistant PTSD of at least six months duration. The open label lead-in, Stage 1 (the randomized, double-blind, active-placebo controlled phase) and Stage 2 (the open label phase) will all follow the same basic sequence of events and methods. The schedule will include three separate sessions of MDMA-assisted psychotherapy lasting one day about one month apart (with in a window of 3-5 weeks) with a male/female co-therapist team. 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. 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 the sponsor to ensure proper therapist training and subject safety. The sponsor will review at least three of five experimental sessions, entry criteria, vital signs and side effect data for completed sessions and any adverse events. After review, the sponsor will notify the site when Stage 1 may proceed.

In Stage 1, subjects will be randomly assigned to receive three MDMA-assisted sessions with either a full dose of 125 mg MDMA followed by an optional supplemental dose of 62.5 mg MDMA administered 2.5 hours later, or to an active placebo dose of 40 mg MDMA followed by an optional dose of 20 mg MDMA 2.5 hours later. Those subjects who receive the active placebo dose will be offered an option to enroll in Stage 2 unless at this point they meet any exclusion criteria for Stage 2 participation.

At each visit with the study therapist the subject's general wellbeing will be assessed and CSSRS completed. Adverse Events and Concomitant Medications will be collected as described in Section 8 and 9 of the protocol.

An independent rater will administer all outcome measures from the open label lead-in, Stage 1, Stage 2 and the follow up. The rater will assess PTSD symptoms with the CAPS, subject quality of life with the GAF and symptoms of depression with the BDI-II. Baseline assessments of symptoms of PTSD, depression and quality of life ratings will be compared with assessments made two months after the third experimental session in Stage 1. The blind will be broken for all subjects in Stage 1 after completing this assessment. Subjects 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 in Stage 2.

All subjects will complete a one-year follow-up occurring 12 months after their final experimental session. At the 12-month follow-up outcome measures and a questionnaire on study participation will also be administered.

5.1 Planned Duration of Protocol

Subjects enrolled in this study will fall into three categories that will determine the duration of the study for them. These timelines include screening and the follow-up portion of the study.

- Open label lead-in subjects: 16 months
- Stage 1 only subjects: 16 months
- Stage 1 subjects who continue to Stage 2: 21 months

5.2 Randomization and Subject Numbering

The first two subjects will be enrolled in the open label lead-in study, and assigned to the full dose condition. Ten subjects will be enrolled in the randomized Stage 1. Stage 1 will be blinded and there will be a 7/3 ratio between subjects in the Full Dose and Active Placebo conditions. A staff member of the Sponsor will serve as an unblinded randomization monitor. The randomization monitor will generate the randomization list. Subjects will be assigned subject numbers in ascending order in a blinded fashion to the next available randomization number. The randomization numbers will be pre-printed on the drug packaging labels. Randomization will be performed at least 24 hours before the first experimental session for each subject. The investigators will contact the randomization monitor to obtain the randomization number for each experimental session. All study evaluations in the randomized portion of the study will be done by blinded personnel until the unblinding of each subject at the end of Stage 1. Detailed instructions will be provided to the site in a separate document.

Individuals who replace subjects who withdraw from the study will be assigned the next available subject number. If the withdrawal occurs after the blind is broken, the site should contact the randomization monitor for replacement instructions. If there is an emergency requiring knowledge of subject's condition assignment, the blind may be broken for an individual subject. The randomization monitor will provide the investigator with sealed emergency unblinding envelopes corresponding to each randomization number. These sealed envelopes will be stored in a secure limited access area and should remain sealed if there are no emergency unblinding events during the study. The investigators, independent rater, study staff and the subject will remain blind to randomization assignment until unblinding at the end of Stage 1. Unblinding at the end of Stage 1 should be done via communication with the randomization monitor. Detailed instructions will be provided to the site in a separate document.

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.

Subjects in the open label lead-in (the first two subjects) and Stage 2 open label section (active placebo subjects from Stage 1) will all be assigned to the full dose condition, and the subject, the investigators and the independent rater will be aware of condition assignment in Stage 2.

5.3 Recruitment and Subject Population

Enrollment for the study is planned to be twelve subjects who have been diagnosed with PTSD of at least six months duration that have not responded to prior treatment. Subjects must be at least 18 years old with a diagnosis of PTSD and a CAPS score greater than or equal to 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 subjects 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, a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) 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 the subject is concurrently seeing an outside therapist) including any experimental therapies.
8. Agree to, for one week preceding each MDMA 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 24:00 (midnight) the evening before each experimental session. Subjects 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. Subjects must agree not to use caffeine or nicotine for 1 hour before and 3 hours after ingesting the drug, or until the investigators deem it safe to do so.
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 subjects of childbearing potential, must be willing to have pregnancy tests and must agree to use an effective form of birth control.
14. Are literate. Subjects must be proficient in reading documents written in Arabic, and they must be able to effectively communicate with the therapists and other site personnel.
15. Must be willing not to participate in any other clinical trial for the duration of this clinical trial, including the follow up period.

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. Are 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. (Subjects 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 psychiatric drug, including SSRIs, SNRIs, or MAOIs.
10. Meet DSM-IV criteria for substance abuse or dependence for any substance other than 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, subjects 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. The Independent Rater will administer the Structured Clinical Interview for DSM-IV (SCID) and assessment via Clinician-Administered PTSD Scale (CAPS) for psychiatric diagnosis to determine subject eligibility. If, after reviewing all information, the investigators conclude that a subject

is eligible, they will enroll the subject in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

If medication tapering is necessary, the first experimental session will be scheduled to occur after washout is complete. After undergoing three preparatory psychotherapy sessions with a male/female co-therapist team lasting at least an hour, the lead-in study subjects will undertake three experimental sessions with full dose MDMA. Each experimental session will be scheduled approximately three to five weeks apart and will last about 8 hours. The day after the experimental session, subjects will have an additional non-drug psychotherapy session followed by daily phone calls for seven days and integrative psychotherapy sessions on a weekly basis. In Stage 1, the remaining ten subjects will be randomized to receive either full or active placebo dose of MDMA and will follow the same visit schedule. In Stage 2, active placebo subjects will be offered full dose MDMA according to the same schedule of events.

Subject PTSD symptoms will be assessed using the CAPS by an independent rater who will be blind to condition assignment and not present during any of the psychotherapy sessions. The rater will assess PTSD symptoms at baseline as a criterion for enrollment, 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 subject on the GAF, a scale that assesses global quality of life and psychological function, at the same time points listed above. Subjects will also complete the BDI-II, a self-report measure of symptoms of depression, at baseline, two months after the third experimental session and at 12 month follow up.

All psychotherapy sessions, including MDMA-assisted sessions, will be recorded to audio and video, with all recordings preserved for research purposes, and subjects 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. Subjects will rate their current degree of subjective distress with a single-item, self-reported measure, 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 CAPS, a clinician-scored measure for PTSD diagnosis and measure of symptom intensity and severity. The CAPS will be performed by a blinded independent rater who will never be present during the subjects' experimental sessions nor have any information regarding the experimental sessions. Subjects will be instructed not to tell the independent rater any beliefs they or others have concerning their

condition assignment during the evaluation session. The CAPS provides a standardized method 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 [75, 76]. An independent rater will assess all subjects at study baseline and two months after the third experimental session. The independent rater will assess all subjects enrolled in Stage 2 two months after their third open label session, and 12 months after the subject's final experimental session.

The Beck Depression Inventory-II (BDI-II) is a 21-item self-report measure of depressive symptoms [77, 78] that will serve as a measure of depression. It takes five to ten minutes to complete. An Arabic translation of the measure exists [79]. Subjects will complete the BDI-II at the same times when the CAPS will be administered.

The Reactions to Research Participation Questionnaire (RRPQ) [80] is an assessment of causes for taking part in research and responses to the experience of being a research subject. Subjects will complete this measure during their final study visit, with exact time of completion varying in accordance with subject enrollment in the open label study segment or in the third open label MDMA-assisted psychotherapy session in Stage 2. The RRPQ is intended to assess the subject's experience as a research subject, perceived reasons for consenting to be a research subject and perceived freedom to take part in the study, 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 subjects at baseline and two months after the third experimental or open label session. Subjects enrolled in Stage 2 will be assessed on the GAF two months after the third open label Stage 2 session and at 12-month follow-up.

6.1.2 Safety Measures

Safety measures, vital signs and a measurement of psychological distress will be assessed during both experimental sessions. Subjects will rate their current degree of subjective distress with a single-item, self-report scale, the SUD scale, repeatedly during both experimental sessions, 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 [81]. It consists of a "Baseline" form that assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions, and can be administered during a face-to-face interview or over the telephone. The C-SSRS will be administered up to 24 times during the open label lead-in and Stage 1; at baseline, after the second preparatory session, before and six hours after each

experimental session, after each integrative session, on the first and last days of daily telephone contact after an experimental session, and two months after the third experimental session. Subjects who are discontinuing medication to participate in the study will complete the C-SSRS before and after medication washout.

The investigators will also assess general wellbeing during each introductory session, on each integrative session and integrative telephone calls for seven days.

Blood pressure and heart rate will be assessed periodically during each experimental session. Blood pressure and pulse will be measured at the outset of the experimental session, and once approximately every 30 minutes during the experimental session. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic or pulse of 110 are exceeded. The investigators will measure subject body temperature via tympanic thermometer every approximately 60 to 90 minutes. Cardiovascular effects will be assessed via blood pressure measurement. Body temperature will be assessed via tympanic thermometer. The timing of these measurements will be adjusted so they do not interfere with the therapeutic process.

All adverse events and spontaneously reported side effects will be collected during each experimental session and for 7 days after each session. 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. Adverse events requiring medical attention will be collected from the first experimental session to the subject's last 2-month follow up. Serious adverse events (SAEs), adverse events leading to subject withdrawal from the study, and changes to psychiatric status will be collected throughout the protocol. Medications used to treat the specified adverse events will be collected during the study, and all changes to psychiatric medications will be collected throughout the study.

Table 1. Time & Events Stage 1	**Screen**	**Preparatory**		**Experimental Session 1**		**Experimental Session 2**		**Experimental Session 3**		**2 Month Follow-Up**		**12 Month Follow-Up**
Visit #	Pre-Study	V1	V 2,3,4	V5	V 6,7,8	V9	V 10,11,12	V13	V 14,15,16	V17		12 Month
Type of Visit	Screening	Baseline	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Experimental Session 3	Integrative Sessions	2 month Outcome		Follow up & Outcome and Termination
Visit Timing or Study day or Window	Up to 1 month before V1, can be over >1 day	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	Can be over > 1 day, 2 month post V13		Can be over > 1 day, 12 months post V13
Informed Consent	X											
Medical/Psychiatric History	X											
General Physical Exam, ECG	X											
Brief Neurological Exam	X											
SCID	X											
Clinical Lab Tests, w/ HIV test	X											
Collect Concomitant Medication	X	X	X	X	X	X	X	X	X	X		X
Medication Taper (if applicable)	X	X										
Drug Screen	X			X		X		X				
Pregnancy Screen (if applicable)	X			X		X		X				
CAPS, GAF, BDI-II (Ind. Rater)	X	X[A]								X		X
Study Enrollment		X										
Record to Audio/Video			X	X	X	X	X	X	X			
General Well-Being		X	X	X	X	X	X	X	X	X		X
Complete Randomization				X[B]								
C-SSRS		X	X[G]	X[C, D, E]	X[I]	X[C, D, E]	X[I]	X[C, D, E]	X[I]	X		X
Administer IP Drug + Therapy				X		X		X				
Monitoring of BP, Pulse, Temp.				X		X		X				
SUD				X[D, F]		X[D, F]		X[D, F]				
Belief of Condition Assignment[L]					X		X		X	X		
Overnight Stay				X		X		X				
Integrative Therapy Session					X[I]		X[I]		X[I]			
7 days Integrative Phone Contact					X		X		X			
AEs Requiring Medical attention				X	X	X	X	X	X	X		
Spont. Side Effects and all AEs[K]				X	X	X	X	X	X			
AEs related to changes in psychiatric status or withdrawal		X	X	X	X	X	X	X	X	X		X
Serious Adverse Events		X	X	X	X	X	X	X	X	X		X
RRPQ										X[H]		
Follow up Questionnaire												X[H]
Unblinding[J]										X		
Issue Memory Aid Card[H]										X		
Study Termination[J]												X

End of Stage 1: Go to Stage 2 **or** 12 month Follow Up Outcome and Termination

A = repeat before V5 ONLY if meds are tapered B = Within 24 hrs prior to V5 C =Approximately 6 hours post MDMA D =at the beginning of the session E =as needed F =Approximately every 60 minutes G =Given on V3 only H = Only for subjects not going to Stage 2 I=For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days J =Determine: Termination at Stage 1 or go on to Stage 2 K= Collected on the day of MDMA administration and for seven days after each Exp. Session L= At 1st integrative visit after each Exp. Session for subjects & investigators and at V17 for the independent rater.

Table 2. Time & Events Stage 2	**Preparatory**	**Experimental Session 1**		**Experimental Session 2**		**Experimental Session 3**		**2 Month Follow-Up**		**12 Month Follow Up**
Visit #	V18*	V19	V 20,21,22	V23	V 24,25,26	V27	V 28,29,30	V31	**End of Stage 2:** Go to 12 Month Follow Up Outcome and Termination	12 Month
Type of Visit	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Experimental Session 3	Integrative Sessions	Follow-Up & Outcome		Follow up and Outcome and Termination
Visit Timing or Study day or Window	Within 1 month of V17*	1 week post V18	Approx. 1 week apart	3-5 weeks post V19	Approx. 1 week apart	3-5 weeks post V23	Approx. 1 week apart	May occur over >1 day 2 mo. post V28		May occur over >1 day 12 mo. post V28
Confirm Informed Consent	X									
Confirm Inclusion/Exclusion	X									
Enrollment in Stage 2	X									
Collect Concomitant Medication	X	X	X	X	X	X	X	X		X
Record to Audio/Video	X	X	X	X	X	X	X			
General Well-Being	X	X	X	X	X	X	X	X		X
Drug Screen		X		X		X				
Pregnancy Screen (if applicable)		X		X		X				
CAPS, GAF, BDI-II (Ind. Rater)	Use V17[A]							X		X
C-SSRS	X	X[C, D, E]	X[H]	X[C, D, E]	X[H]	X[C, D, E]	X[H]	X		X
Administer IP Drug+Therapy		X		X		X				
Monitoring of BP, Pulse, Temp.		X		X		X				
SUD		X[D,F]		X[D, F]		X[D, F]				
Overnight Stay		X		X		X				
Integrative Therapy Session			X		X		X			
7 days Integrative Phone Contact			X[I]		X[I]		X[I]			
AEs Requiring Medical attention	X	X	X	X	X	X	X	X		
Spont. Side Effects and all AEs[K]		X	X	X	X	X	X			
AEs related to changes in psychiatric status or withdrawal	X	X	X	X	X	X	X	X		X
Serious Adverse Events	X	X	X	X	X	X	X	X		X
Complete Stage 2 go to 1yr Follow-up								X		
RRPQ								X		
Follow up Questionnaire										X
Issue Memory Aid Card								X		
Termination Visit										X

A= Re-baseline if V18 is more then 1 month after V17 C =Approximately 6 hours post MDMA D =at the beginning of the session E =as needed F = Approximately every 60 minutes H= On Day 2 and Day 7 of phone calls after experimental sessions I = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days K= Common expected side effects will be collected on the day of MDMA administration and for seven days after each Exp. Session.

6.2 Visit Descriptions

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

Once a subject gives written informed consent, a screening number will be assigned. The screening number will be used on all subject records prior to enrollment. Subjects will provide a self-reported medical and psychological history including past and current use of medication 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 subject medical records and request additional tests or assessments as indicated.

An independent rater will perform the Structured Clinical Interview for Diagnoses (SCID) to assess study eligibility. The independent rater will not be present during any of the therapy sessions and will administer the CAPS, the GAF and the BDI-II. The C-SSRS will also be administered at screening to assess suicide risk.

After eligibility is confirmed the subject will be considered enrolled and will be issued a subject number. The investigators will review this information and will contact the subject 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. Once a subject is enrolled Adverse Events and Medications will be collected as described in Sections 8 and 9 of the protocol. Any subject 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. Subjects who require medication washout will be assessed via CAPS, BDI-II 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 subject's health and well being to ensure that subject continues to meet eligibility criteria and if applicable, will confirm that they have appropriately tapered off of medications.

The subject will undergo three sixty to ninety minute introductory sessions with the investigators, who will be a male and a female co-therapist team. The investigators will work with the subject to prepare him or her for MDMA-assisted psychotherapy. The investigators and subject will seek to form a strong working relationship with each other, and they will help the subject prepare for upcoming experimental sessions. Introductory sessions will promote a safe space for confronting trauma-related memories, emotions and thoughts. The subject 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 subject to prepare him or her for MDMA-assisted psychotherapy.

During the third and last introductory session, the investigators will supply the subject with a set of instructions and restrictions for conduct 24 hours prior to receiving MDMA, including restrictions on food and alcohol consumption. Subjects must agree to take nothing by mouth except alcohol-free liquids after 24:00 (midnight) the evening before the MDMA session. Subjects must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA session. Subjects must agree not to use caffeine or nicotine for 1 hour before and 3 hours after ingesting the drug, or until the investigators deem it safe to do so.

The investigators will introduce the subject to the attendant during one of the preparatory sessions. The attendant, described below, will remain with the subject 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 subject. If a subject 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 subject is still undergoing medication washout, subjects will complete the C-SSRS just prior to beginning the second preparatory session. Subjects 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 subjects can receive copies of these sessions upon request.

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

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

All subjects in Stage 1 receive three double blind experimental sessions of MDMA-assisted psychotherapy scheduled 1 month (three to five weeks) apart, and subjects in the open label lead-in and open label Stage 2 will receive three sessions with the full dose of MDMA. Subjects assigned to Full Dose will receive 125 mg MDMA possibly followed by 62.5 mg MDMA during all experimental sessions, and subjects 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 team. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions, and all procedures except drug dose will be the same for subjects assigned to the full and active placebo dose conditions. Subjects in the open label lead-in and open label Stage 2 will receive three sessions that employ the experimental dose of MDMA.

At least 24 hours prior to the first experimental session the subject randomization will be completed.

On the day of the experimental session, the subject 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 childbearing potential, a urine pregnancy test will be performed. If the subject continues to meet criteria and the subject reports that he/she followed appropriate rules and restrictions, the session will proceed; a positive pregnancy screen is cause for withdrawal from the study, 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 subject from the study.

The investigators will review procedures for the MDMA session with the subject. The investigators will record the entire session to video and audio. Subjects 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 investigators and subject will discuss and review the subject's goals, intentions and concerns and some of the commonly experienced effects of MDMA. Subjects will complete the SUD just prior to initial dose administration.

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

At approximately 10:00 in the morning, subjects will receive the initial dose of MDMA along with a glass of water. The subject will sit or recline on comfortable furnishings, and there will be eyeshades and a program of music available if the subject 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 [82-84]. The investigators will also encourage periods of time in which the subject 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. 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 subject 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 subject has not spoken spontaneously, the investigators will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the investigators will support and encourage the subject 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. Subject body temperature will be measured via tympanic thermometer and subjects will complete the SUD 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 subject 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. Subject acclimated to environment, C-SSRS
9:45	Baseline BP, Pulse, Subjective Units of Distress Rating (SUD)
9:55	2nd Baseline BP, Pulse, BT, SUD
10:00	**Drug Administration**, begin recording to audio and video
10:30	BP, Pulse.
11:00	BP, Pulse, SUD, BT
11:30	BP, Pulse; **Can administer optional supplemental dose**
12:00	BP, Pulse, BT
12:30	BP, Pulse, SUD
13:00	BP, Pulse
13:30	BP, Pulse, BT
14:00	BP, Pulse, SUD
Every hour, and as needed	BP, Pulse,
Every 60-90 minutes	SUD, Temp
Approximately 6 hours after drug administration	C-SSRS, General Wellbeing

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

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

A supportive individual who has previously agreed to remain with the subject during the MDMA session may arrive during the session if the therapists agree.

The investigators will remain with the subject 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 subject 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 subject is emotionally and medically stable. During the experimental session and for one week after, site personnel will remain available to subjects via 24-hour cellular phone.

Subjects will be instructed not to use caffeine or nicotine for 1 hour before and 3 hours after ingesting the drug, or until the investigators deem it safe to do so. Spontaneously reported side effects and all AEs will be collected starting on the day of the MDMA session through the seventh daily telephone call.

Subjects will remain overnight in an appropriately furnished room at the study site. With the approval of the therapists, a significant other may accompany the subject during the overnight stay. A same-sex attendant will check in periodically on the subject during the overnight stay, even if a companion is present. The attendant will monitor subject health and will help subjects 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 subject needs additional support, the attendant can contact the investigators. The subject and and a companion (if applicable), will receive information that will allow them to contact the investigators during the overnight stay in the case of an emergency or request for additional support. Subjects will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

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

6.2.4 Integrative Sessions 24 Hours after Experimental Session (Visits 6, 10, 14)
On the morning after each experimental session, the subject will meet with both

investigators during a 90-minute integrative therapy session. Subjects will complete the C-SSRS just prior to beginning each integrative session. General wellbeing will also be assessed. Prior to integrative psychotherapy, the subject and both investigators will indicate their beliefs concerning subject condition assignment. During the integrative session, the subject and investigators will discuss and review events, thoughts, feelings and memories that occurred during the experimental session. If necessary, the investigators will help the subject to reduce any residual psychological distress he or she is experiencing. The investigators will also encourage the transfer of states of acceptance, feelings of intimacy, closeness and reduced fear experienced in MDMA sessions to emotionally threatening everyday situations. The investigators will be supportive, validating the MDMA experience and facilitating understanding and emotional clearing. The investigators should be accessible any time the subject needs support outside the scheduled integration sessions. The investigators will assess subject 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 investigators to gather information about the effects of MDMA on the subject in an unstructured manner. After this psychotherapy session, a person previously selected will provide a ride home. If the subject is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the subject due to unforeseen events, the investigators will assist the subject in finding an alternative means of returning home. The entire integrative psychotherapy session will be recorded to audio and video. Subjects may receive copies of this session upon request.

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

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 subject via telephone on a daily basis for one week. The integrative telephone contact will be for a brief check-in lasting as long as necessary to address any subject's concerns and to assess subject wellbeing. Additional telephone contact can be initiated at the request of the investigators or subject. On the second and seventh day contact after the experimental session, the subject will complete the C-SRRS over the telephone.

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

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

The subject will have three 60 to 90-minute non-drug psychotherapy sessions with both investigators after each experimental session. The investigators may conduct more sessions if they and the subject deem it necessary. The subject and investigators will continue to work on supporting the subject as they consider his or her experiences during experimental sessions. The investigators will use clinical judgment to assess the subject's

psychological wellbeing during this period of time. If there are any indications of continuing anxiety or distress, the investigators may arrange to work on reducing the distress at a specially scheduled non-drug therapy session, through continuing contact, or at the next regularly scheduled non-drug therapy session. The subject may also initiate contact with the investigators at any time throughout the study. Each integrative session will be recorded to audio and video, and subjects may receive a copy of one or more integrative sessions upon request. All sessions will be recorded to audio and video.

The C-SSRS will be administered just prior to beginning each integrative session. 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.

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

6.2.7 Evaluation Two Months after the Third Experimental Session and Unblinding (V17)

The final evaluation in the double blind portion of the study will occur two months after the third experimental session. This visit will consist of two meetings that may be completed on separate days, one with the independent rater and the other with the investigators. During the first meeting, the independent rater will administer CAPS to assess PTSD symptoms, quality of life with the GAF, and depression with the BDI-II. The independent rater will provide their belief of each subject's condition at this visit. After completing all assessments and measures, the subject will meet with the investigators. The investigators will administer the C-SSRS to assess suicidality. The blind will be broken for the subject's condition assignment.

If the subject has received active placebo in Stage 1, the investigators will discuss enrollment in Stage 2. (see section 6.2.8)

If the subject has received full dose MDMA in Stage 1 or the open label lead-in, or they elect not to participate in Stage 2, they will complete the Responses to Research Participation Questionnaire (RRPQ) and continue on to the 12-month Follow Up visit and study termination.

Subjects not moving on to Stage 2 will receive a memory aid card for use between this visit and the 12-month follow up. Subjects will use this card to record AEs, medications and changes in psychiatric status that they will be asked about at the termination visit. Memory Aids will not be collected. Full dose subjects may return to taking psychiatric medications from this point onward if necessary.

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

6.2.8 Open label "Stage 2" for Active Placebo Subjects

Active Placebo subjects 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 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 then 30 days from the time of the last CAPS in Stage 1 the independent rater will re-administer the CAPS, BDI-II and GAF and these scores will be used as the baseline for comparison to assessment after final open label session in Stage 2.

Subjects enrolled in Stage 2 will meet with both investigators for at least a single review and introductory psychotherapy session, followed by an open label MDMA-assisted therapy session. Subjects will have the same sequence of sessions and integrative therapy as in Stage 1. Visits will be scheduled according to the Time and Events Table 2. 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, SAEs and medications will be collected and reported in the same manner as during the randomized study segment.

6.2.9 Evaluation Two Months after Third Open label Session

Treatment effects in Stage 2 will be assessed two months after the third experimental session. This visit will consist of two meetings that may be completed on separate days, one with the independent rater and the other with the investigators. During the first meeting, the independent rater will administer CAPS to assess PTSD symptoms, quality of life with the GAF, and depression with the BDI-II. After completing all assessments and measures, the subject will meet with the investigators. The investigators will administer the C-SSRS to assess suicidality. General wellbeing will be assessed. Subjects will complete the Responses to Research Participation Questionnaire (RRPQ).

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

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

6.2.10 Evaluation 12 Months After Final Experimental Or Open Label Session

All subjects who completed the lead-in, Stage 1 and Stage 2 will be evaluated for long-term effects 12 months after their last MDMA-assisted psychotherapy session. This visit will consist of two meetings, one with the independent rater and the other with the investigators. The independent rater will administer the CAPS, BDI-II and the GAF.

Subjects will have a final meeting with the investigators to review specified AEs and medications since the last visit and to complete the termination visit. The investigators will assess suicidality with the C-SSRS. Subjects will also complete a questionnaire assessing positive and negative long-term effects of the study.

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

6.3 Removal of Subjects from the Study

Subjects can withdraw consent at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with elements of experimental sessions and related visits that are critical for safety. If the investigator withdraws a subject from the session, the investigators will explain the reason for withdrawing the subject.
If a subject develops any exclusion criteria that in the opinion of the Medical Monitor, affects the safety of the subject, including psychiatric diagnosis, pregnancy or excluded medications, the subject may be removed from the study.

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

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

In preparation for MDMA sessions, blood draws and a full medical examination are required to establish eligibility for the study. Temporary discomfort, inflammation or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

During screening, non-drug and MDMA-assisted psychotherapy sessions and assessment of study measures, subjects will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy, experimental and open label sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention (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. Subjects may feel uncomfortable with having their sessions recorded. The recordings will be used for developing a manualized form of MDMA-assisted psychotherapy, and subjects may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment. Subjects will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by investigators or regulatory agencies.

7.2 Risks of Receiving MDMA

Side effects of MDMA are modest and have generally not been associated with serious discomfort by healthy volunteers in previous studies. Common side effects include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common side effects include restlessness, parasthesias (odd somatic feelings, such as tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, and nystagmus (eye-wiggling). These effects are transient and diminish 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 described in the Investigator's Brochure.

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. Previous Phase 1 studies have not reported any indication of increased risk of illness occurring after MDMA administration.

MDMA may produce mild alterations in sensory perception and altered perception of time [44, 56, 71]. Women may be more sensitive to these effects [59]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change [49].

7.2.1 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 subjects 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 [62, 71]. In MP-1, elevation in blood pressure and heart rate after the supplemental dose did not exceed elevations seen after the initial dose. No subjects in MP-1 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. The active placebo dose of MDMA may produce a slight elevation in blood pressure and heart rate [58].

7.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported 1–3 days after MDMA administration [58, 59, and see the IB]. Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the 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 subjects having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from the investigator, with occasional use of benzodiazepines for anxiety. In the proposed study, subjects will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties subjects might have with acute or sub-acute side effects. 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)
- preparatory non-drug psychotherapy sessions before the experimental session
- creating an atmosphere of trust during the experimental session
- close monitoring
- daily contact with subjects for the period of a week after the experimental session
- providing non-drug integrative psychotherapy sessions
- Subjects will remain at the study site for the night of each experimental session to further reduce psychological distress. Qualified personnel will be available during the overnight stay to respond to the needs of the subject. Attendants will be instructed to contact the investigator upon request or at the appearance of signs of a potential adverse event.

During the preparatory sessions, subjects 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 subjects 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 subjects.

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

- If the subject is anxious, agitated, in danger of any self-harm or is suicidal at the end of the MDMA session, the investigators will remain with the subject for at least two more hours. During this time, the investigators will employ affect management techniques, will talk with the subject to help him or her gain cognitive perspective of their experiences, and will help them implement the self-soothing and stress inoculation techniques presented during the 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 subject for at least two additional hours.

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

    B. If a subject experiences 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 the concomitant medications CRF page. Investigators should not prescribe an SSRI, SNRI or MAOI in this context. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

    C. Hospitalization for stabilization. If a subject should become psychotic arrangements will be made to stabilize them and transfer them to the Al-Rashid ICU if necessary.

Subjects 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 subject's emotional status.

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

7.2.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [59], 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 subjects 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.

7.2.4 Abuse Liability

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.

7.2.5 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 [85, 86], 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.

7.3 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 sponsor has established contingency plans for responding to those AEs that appear most likely, based on a comprehensive review of literature described in the current Investigator's Brochure. The same contingency plans and equipment will be used in this protocol. In the event of a medical emergency, with these personnel and equipment, the investigators will be able to stabilize study subjects and then transport them to the ICU at the Al-Rashid Hospital if necessary.

8.0 Adverse Events

8.1 Adverse Events

Adverse Event (AE) - Any untoward or unfavorable medical occurrence in a clinical research study subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subjects' 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 reported side effects will be collected during the experimental session and the seven days of telephone contact following 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 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 the sponsor. A fax number will be provided to the site in separate site-specific instruction for SAE reporting. In addition to the fax, the PI should call the CRA during normal working hours and verbally inform the CRA of the SAE. During off hours or if medical advice is needed immediately please call the sponsor Medical Monitor. An SAE reporting instruction with all contact numbers will be provided to the site prior to study start.

Medical Monitor:

Michael C Mithoefer
Email: mmithoefer@mac.com
Telephone: 00-1-843-849-6899
Fax: 00-1-843-278-9188

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

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

- All SAEs will be collected through termination.
- All Adverse Events and common expected side effects will be collected on the day of MDMA administration and for seven days after each experimental session.
- Events requiring medical attention will be collected from the first experimental session through the subject's last 2-month follow up.
- Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any Adverse Event leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

A subject memory aid card will be provided to the subject on the last visit prior to the 12 month follow up to record information on medications and AEs during the period between the final visit and the 12 month follow up evaluation. The memory aid card will not be collected, but information from the card will be used to aid the subjects in providing information to the investigator. This information may be collected by phone.

9.0 Concomitant Medications and Tapering Instructions

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

prospective subject will be encouraged to discuss 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. All medications, over the counter (OTC) and prescription will be collected from screening through 7 days after the last MDMA session. From 7 days after the last MDMA session through study termination only prescription or OTC medications taken to treat AEs will be collected. Throughout the protocol all medications used to treat AEs will be collected as specified in Section 8 and all changes including discontinuations or additions to psychiatric medications will be collected. Medications taken during the course of the protocol will be recorded on the concomitant medications CRF.

Subjects must be willing to refrain from taking any psychiatric medications during Stage 1 and Stage 2, with the exception of gabapentin when prescribed for pain control.

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

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

a. They will refrain from taking any herbal 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).

Subjects will receive a memory aid card for use between the 2-month assessment visit and the 12-month follow up. Subjects will use this card to record changes in psychiatric medications that they will be asked about at the termination visit. Memory aids will not be collected. Subjects may return to taking psychiatric medications after the 2-month assessment if necessary.

10.0 Clinical Laboratory Assessments

The principal investigator will examine laboratory assessments gathered in screening for assessing subject eligibility. The investigator will use a list of normal ranges to conclude whether subjects are eligible for the protocol, and will indicate justification for admitting subjects 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;
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
Al-Rashid Hospital
PO Box 540851 Abu Nsair
Amman, Jordan 11937

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

11.0 Study Monitoring, Auditing and Documentation

Investigators and their study staff will be trained prior to the start of the protocol. The study site will be monitored by site visits and telephone calls to the investigator by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. 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 subject 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. For detailed monitoring information, please see the MP-7 Monitoring Plan.

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 sponsor will conduct data analysis for the study. The sponsor will examine data on the effects of active placebo versus full 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 full dose) as a between-subjects variable and time of administration (baseline versus two months after third experimental session) as a repeated measure. The sponsor 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 sponsor 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 sponsor will examine the effects of active placebo versus full dose MDMA-assisted psychotherapy on symptoms of depression and quality of life through performing between subjects / within-subjects ANOVAS on BDI-II 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 sponsor may also perform a comparison of baseline and two-month follow-up CAPS, GAF and BDI-II scores that will include scores from subjects in the randomized study and the open label lead-in.

The sponsor will perform a comparison of CAPS, GAF and BDI-II scores at baseline and at 12-month follow-up.

There will not be a sufficient number of subjects 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 sponsor 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 the there are no significant differences in measures of safety for open label lead-in and randomized study subjects, then the sponsor will combine safety data from both groups. Data for blood pressure, pulse, body temperature and SUD pre-drug administration baseline, approximately three hours after initial dose administration, seven hours after initial dose administration and peak values will be collected on case report forms. The sponsor will compute descriptive statistics for these variables. Though formal analyses will not be possible for subjects in Stage 2, descriptive statistics for all safety measures will be collected for Stage 2 subjects.

An interim analysis may be completed when all subjects have completed the main study, including Stage 1 and Stage 2, but not all subjects have completed the 12-month follow-up evaluation. Additionally, an interim analysis may be performed after all subjects have completed Stage 1 but not necessarily before all eligible subjects complete Stage 2.

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 subjects with PTSD was calculated to be 1.1 (Mithoefer et al. Unpublished). The sponsor intends to conduct meta-analyses of data 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 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 [87]. 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 local 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 by signing the consent form. 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 person obtaining the consent.

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

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF 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 effect 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 subjects in their role as research subjects. Despite this, absolute privacy cannot be guaranteed. Data collected from each subject will be identified only by the subject's initials and by a subject number on the source documents. All study measures, records, audio and video recordings will be kept in a locked file drawer in a locked office. Access to study measures will be limited to regulatory agencies, researchers assessing the subject for changes in symptoms, sponsor representatives, and individuals analyzing data. Researchers with access to data

will not be provided with any information that would identify subjects by name or by other means.

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

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

13.2 Costs to Subjects

The sponsor of this study will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions, for the psychological and laboratory testing, for medical examinations, for the study drug and for any rescue medications used during the study. The subject, 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 subject or their private insurance remains responsible for ongoing 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 will cover any costs that arise from treating the injury. The sponsor has an insurance policy to cover the subjects' from any disabilities resulting from the study procedures. The subject will be compensated according to the level of disability arising from medication or procedures used in the study. This insurance 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 applicable ICH-GCP and local regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the ISF. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

References

1. Kessler, R.C., et al., *Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry, 2005. **62**: 593-602.
2. Brunello, N., et al., *Posttraumatic stress disorder: diagnosis and epidemiology, comorbidity and social consequences, biology and treatment.* Neuropsychobiology, 2001. **43**: 150-62.
3. Norris, F.H., et al., *Epidemiology of trauma and posttraumatic stress disorder in Mexico.* J Abnorm Psychol, 2003. **112**: 646-56.
4. Perkonigg, A., et al., *Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity.* Acta Psychiatr Scand, 2000. **101**: 46-59.
5. Sareen, J., et al., *Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions.* Arch Intern Med, 2006. **166**: 2109-16.
6. Zlotnick, C., et al., *Epidemiology of trauma, post-traumatic stress disorder (PTSD) and co-morbid disorders in Chile.* Psychol Med, 2006. **36**: 1523-33.
7. Hoge, C.W., et al., *Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care.* N Engl J Med, 2004. **351**: 13-22.
8. Tanielian, T.L., L. Jaycox, and Rand Corporation., *Invisible wounds of war : psychological and cognitive injuries, their consequences, and services to assist recovery*. 2008, Santa Monica, CA: RAND. xliii, 453 p.
9. *Statement Of Jon A. Wooditch Acting Inspector General Department Of Veterans Affairs*, in *Committee On Veterans' Affairs Subcommittee On Disability Assistance And Memorial Affairs*. 2005: Washington, DC.
10. de Jong, J.T., I.H. Komproe, and M. Van Ommeren, *Common mental disorders in postconflict settings.* Lancet, 2003. **361**: 2128-30.
11. Thabet, A.A. and P. Vostanis, *Post-traumatic stress reactions in children of war.* J Child Psychol Psychiatry, 1999. **40**: 385-91.
12. Weine, S.M., et al., *Psychiatric consequences of "ethnic cleansing": clinical assessments and trauma testimonies of newly resettled Bosnian refugees.* Am J Psychiatry, 1995. **152**: 536-42.
13. Kessler, R.C., et al., *Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry, 2005. **62**: 617-27.
14. Breslau, N. and G.C. Davis, *Posttraumatic stress disorder in an urban population of young adults: risk factors for chronicity.* Am J Psychiatry, 1992. **149**: 671-5.
15. Breslau, N., *The epidemiology of posttraumatic stress disorder: what is the extent of the problem?* J Clin Psychiatry, 2001. **62 Suppl 17**: 16-22.
16. Frayne, S.M., et al., *Burden of medical illness in women with depression and posttraumatic stress disorder.* Arch Intern Med, 2004. **164**: 1306-12.
17. Brady, K.T., T.S. Charney, and J.R.T. Davidson, *Current Issues in the Management of Posttraumatic Stress Disorder.* 2000, Littleton, CO.: Medical Education Resources.

18. Kessler, R.C., et al., *Posttraumatic stress disorder in the National Comorbidity Survey.* Arch Gen Psychiatry, 1995. **52**: 1048-60.
19. Resick, P.A., et al., *A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims.* J Consult Clin Psychol, 2002. **70**: 867-79.
20. Hamner, M.B., S. Robert, and B.C. Frueh, *Treatment-resistant posttraumatic stress disorder: strategies for intervention.* CNS Spectr, 2004. **9**: 740-52.
21. Montgomery, S. and P. Bech, *ECNP consensus meeting, March 5-6, 1999, Nice. Post traumatic stress disorder: guidelines for investigating efficacy of pharmacological intervention. ECNP and ECST.* Eur Neuropsychopharmacol, 2000. **10**: 297-303.
22. Foa, E.B., et al., *A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims.* J Consult Clin Psychol, 1999. **67**: 194-200.
23. Resick, P.A. and M.K. Schnicke, *Cognitive processing therapy for sexual assault victims.* J Consult Clin Psychol, 1992. **60**: 748-56.
24. Brady, K., et al., *Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial.* JAMA, 2000. **283**: 1837-44.
25. Basoglu, M., E. Salcioglu, and M. Livanou, *A randomized controlled study of single-session behavioural treatment of earthquake-related post-traumatic stress disorder using an earthquake simulator.* Psychol Med, 2007. **37**: 203-13.
26. Gerardi, M., et al., *Virtual reality exposure therapy using a virtual Iraq: case report.* J Trauma Stress, 2008. **21**: 209-13.
27. Heresco-Levy, U., et al., *Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder.* Int J Neuropsychopharmacol, 2002. **5**: 301-7.
28. Ursano, R.J., et al., *Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder.* Am J Psychiatry, 2004. **161**: 3-31.
29. Benish, S.G., Z.E. Imel, and B.E. Wampold, *The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: a meta-analysis of direct comparisons.* Clin Psychol Rev, 2008. **28**: 746-58.
30. Greer, G.R. and R. Tolbert, *A method of conducting therapeutic sessions with MDMA.* J Psychoactive Drugs, 1998. **30**: 371-379.
31. Metzner, R. and S. Adamson, *Using MDMA in healing, psychotherapy and spiritual practice*, in *Ecstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA.*, J. Holland, Editor. 2001, Inner Traditions: Rochester VT. p. 182-207.
32. Stolaroff, M., *The Secret Chief Revealed: Conversations with a pioneer of the underground therapy movement.* 2004, Sarasota FL: Multidisciplinary Association for Psychedelic Studies.
33. Widmer, S., *Listening into the heart of things: The awakening of love: On MDMA and LSD: The undesired psychotherapy.* . 1998, Gerolfingen, Switzerland: Basic Editions.
34. Nibuya, M., E.J. Nestler, and R.S. Duman, *Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus.* J Neurosci, 1996. **16**: 2365-72.

35. Gamma, A., et al., *3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans.* Neuropsychopharmacology, 2000. **23**: 388-95.
36. Rasmusson, A.M. and D.S. Charney, *Animal models of relevance to PTSD.* Ann N Y Acad Sci, 1997. **821**: 332-51.
37. Davis, M. and C. Shi, *The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety?* Ann N Y Acad Sci, 1999. **877**: 281-91.
38. Randall, S., et al., *Effects of acute 3,4-methylenedioxymethamphetamine on sleep and daytime sleepiness in MDMA users: a preliminary study.* Sleep, 2009. **32**: 1513-9.
39. Bosker, W.M., et al., *Dose-related effects of MDMA on psychomotor function and mood before, during, and after a night of sleep loss.* Psychopharmacology (Berl), 2010. **209**: 69-76.
40. Bedi, G., et al., *Effects of MDMA on sociability and neural response to social threat and social reward.* Psychopharmacology (Berl), 2009. **207**: 73-83.
41. Bouso, J.C., et al., *MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder.* J Psychoactive Drugs, 2008. **40**: 225-36.
42. Marrone, G.F., et al., *Amphetamine analogs methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) differentially affect speech.* Psychopharmacology (Berl), 2010. **208**: 169-77.
43. Hasler, F., et al., *Investigation of serotonin-1A receptor function in the human psychopharmacology of MDMA.* J Psychopharmacol, 2009. **23**: 923-35.
44. Dumont, G.J. and R.J. Verkes, *A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers.* J Psychopharmacol, 2006. **20**: 176-87.
45. Freedman, R.R., C.E. Johanson, and M.E. Tancer, *Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2005. **183**: 248-56.
46. Johanson, C.E., et al., *Discriminative stimulus effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans trained to discriminate among d-amphetamine, meta-chlorophenylpiperazine and placebo.* Drug Alcohol Depend, 2006. **81**: 27-36.
47. Kolbrich, E.A., et al., *Physiological and subjective responses to controlled oral 3,4-methylenedioxymethamphetamine administration.* J Clin Psychopharmacol, 2008. **28**: 432-40.
48. Kolbrich, E.A., et al., *Plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine after controlled oral administration to young adults.* Ther Drug Monit, 2008. **30**: 320-32.
49. Kuypers, K.P. and J.G. Ramaekers, *Transient memory impairment after acute dose of 75mg 3.4-Methylene-dioxymethamphetamine.* J Psychopharmacol, 2005. **19**: 633-9.
50. Kuypers, K.P. and J.G. Ramaekers, *Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected.* Psychopharmacology (Berl), 2007. **189**: 557-63.

51. Kuypers, K.P., N. Samyn, and J.G. Ramaekers, *MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function.* Psychopharmacology (Berl), 2006. **187**: 467-75.
52. Kuypers, K.P., M. Wingen, and J.G. Ramaekers, *Memory and mood during the night and in the morning after repeated evening doses of MDMA.* J Psychopharmacol, 2008. **22**: 895-903.
53. Kuypers, K.P., et al., *Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night.* Psychopharmacology (Berl), 2007. **192**: 111-9.
54. Ramaekers, J.G., K.P. Kuypers, and N. Samyn, *Stimulant effects of 3,4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal.* Addiction, 2006. **101**: 1614-21.
55. Ramaekers, J.G., et al., *Involvement of Inferior Parietal Lobules in Prospective Memory Impairment during Acute MDMA (Ecstasy) Intoxication: An Event-Related fMRI Study.* Neuropsychopharmacology, 2008.
56. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects [In Process Citation].* J Clin Psychopharmacol, 2000. **20**: 455-66.
57. Grob, C.S., et al., *Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations.* Behav Brain Res, 1996. **73**: 103-7.
58. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2002. **162**: 396-405.
59. Liechti, M.E., A. Gamma, and F.X. Vollenweider, *Gender differences in the subjective effects of MDMA.* Psychopharmacology (Berl), 2001. **154**: 161-8.
60. de la Torre, R., et al., *Non-linear pharmacokinetics of MDMA ('ecstasy') in humans.* Br J Clin Pharmacol, 2000. **49**: 104-9.
61. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
62. Mas, M., et al., *Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans.* J Pharmacol Exp Ther, 1999. **290**: 136-45.
63. Tancer, M. and C.E. Johanson, *Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP.* Drug Alcohol Depend, 2003. **72**: 33-44.
64. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting.* J Psychoactive Drugs, 1986. **18**: 319-27.
65. Cole, J.C., et al., *The content of ecstasy tablets: implications for the study of their long-term effects.* Addiction, 2002. **97**: 1531-6.
66. Grinspoon, L. and J.B. Bakalar, *Can drugs be used to enhance the psychotherapeutic process?* Am J Psychother, 1986. **40**: 393-404.
67. Mithoefer, M., A. Mithoefer, and M. Wagner. *Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in subjects with chronic posttraumatic stress*

disorder. in *24th Annual Meeting of the International Society for Traumatic Stress Studies*. 2008. Chicago, IL.

68. Farre, M., et al., *Pharmacological Interaction Between 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and Paroxetine: Pharmacological effects and pharmacokinetics.* J Pharmacol Exp Ther, 2007.
69. Hernandez-Lopez, C., et al., *3,4-Methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics.* J Pharmacol Exp Ther, 2002. **300**: 236-44.
70. Tancer, M.E. and C.E. Johanson, *The subjective effects of MDMA and mCPP in moderate MDMA users.* Drug Alcohol Depend, 2001. **65**: 97-101.
71. Vollenweider, F.X., et al., *Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers.* Neuropsychopharmacology, 1998. **19**: 241-51.
72. Battaglia, G., et al., *Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites.* Eur J Pharmacol, 1988. **149**: 159-63.
73. Setola, V., et al., *3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro.* Mol Pharmacol, 2003. **63**: 1223-9.
74. Verrico, C.D., G.M. Miller, and B.K. Madras, *MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment.* Psychopharmacology (Berl), 2007. **189**: 489-503.
75. Blake, D.D., et al., *A clinician rating scale for assessing current and lifetime PTSD: the CAPS-1.* . Behav Ther, 1990. **13**: 187-188.
76. Nagy, L.M., et al., *Open prospective trial of fluoxetine for posttraumatic stress disorder.* J Clin Psychopharmacol, 1993. **13**: 107-13.
77. Beck, A.T. and C.H. Ward, *Dreams of depressed patients. Characteristic themes in manifest content.* Arch Gen Psychiatry, 1961. **5**: 462-7.
78. Beck, A.T. and R.A. Steer, *Internal consistencies of the original and revised Beck Depression Inventory.* J Clin Psychol, 1984. **40**: 1365-7.
79. Abdel-Khalek, A.M., *Internal consistency of an Arabic Adaptation of the Beck Depression Inventory in four Arab countries.* Psychol Rep, 1998. **82**: 264-6.
80. Newman, E., et al., *Empirically supported ethical research practice: the costs and benefits of research from the participants' view.* Account Res, 2001. **8**: 309-29.
81. Posner, K., et al., *Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants.* Am J Psychiatry, 2007. **164**: 1035-43.
82. Bonny, H.L. and L.M. Savary, *Music and your Mind*. 1990, Tarrytown NY: Station Hill.
83. Grof, S., *LSD Psychotherapy*. 2000: 1980, Sarasota FL: Multidisciplinary Association for Psychedelic Studies.
84. Unkefer, R.F., *Music Therapy in the Treatment of Adults with Mental Disorders: Theoretical Bases and Clinical Interventions.* . 1990, New York, NY: Schirmer Books.

85. McElhatton, P.R., et al., *Congenital anomalies after prenatal ecstasy exposure [letter]*. Lancet, 1999. **354**: 1441-2.
86. Bateman, D.N., et al., *A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England.* Eur J Clin Pharmacol, 2004. **60**: 635-41.
87. Lenth, R.V. *Java Applets for Power and Sample Size (Computer software).* 2006 [cited 2007 June]; Software allowing computation of power under various circumstances; uses online Java programs on site. http://www.stat.uiowa.edu/~rlenth/Power]. Available from: http://www.stat.uiowa.edu/~rlenth/Power.

Appendix A: Audio and Video Recording

Both experimental and non-drug psychotherapy sessions will be video recorded. Two copies of the video will be made, one to be stored in the ISF, and the other to be sent to 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.

Experimental and non-drug psychotherapy sessions will be audio recorded. The recordings will be saved and kept in a locked office. Two copies of the recordings will be made. One copy will be kept in the ISF, and another copy will be sent to the sponsor. An additional copy may be provided to study subjects of any psychotherapy session. The purpose of this is to enable the subjects to have a recording for their own reference.