

**PROTOCOL MP-9**

IND #63-384

Original Protocol: January 10, 2011  
Amendment 1 Version 1: February 14, 2011  
Amendment 2 Version 1: June 7, 2011  
**Amendment 3 Version 1: March 30, 2015**

**A Randomized, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of  
MDMA-assisted Psychotherapy in People with Chronic, Treatment-Resistant  
Posttraumatic Stress Disorder (PTSD)**

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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
CI	Clinical Investigator (e.g. therapists, co-investigators)
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
ECG/EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
F	Fahrenheit
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
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
MP-1	MAPS' first clinical trial of MDMA-assisted psychotherapy for PTSD
PDS	Posttraumatic Diagnostic Scale
PSQI	Pittsburgh Sleep Quality Index
PTSD	Posttraumatic Stress Disorder
PRN	As needed

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
U.S.	United States of America
WBC	White Blood Cell Count

## **2.0 Introduction, Background and Rationale**

### **2.1 Introduction**

This study is sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a U.S.-based IRS-approved non-profit research and educational organization that sponsors research into the therapeutic potential of MDMA, other psychedelic compounds, and marijuana. MAPS' top priority project is working to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with posttraumatic stress disorder (PTSD). This study is a part of an international, multi-site series of Phase 2 studies designed to evaluate safety and efficacy of MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD for possible use as an approved prescription medication in the U.S., Europe and Israel [1].

MAPS' initial US MDMA/PTSD study has been completed, with promising results published in the Journal of Psychopharmacology [2]. Findings from the long-term follow-up study, evaluating the US subjects at an average of 40 months post-treatment, has shown that the therapeutic benefits have been sustained over time. MAPS' Swiss pilot study was completed in early 2011, with the data currently being prepared for publication. MDMA was administered without evidence of harm and generated promising data about efficacy. MAPS' initial Israeli MDMA/PTSD study enrolled five subjects, with the data summarized in our abbreviated report. Additional pilot studies are underway in the US (in veterans with war-related PTSD) and are in the approval process in Canada and Jordan.

This Phase 2 research study will investigate the safety and efficacy of MDMA-assisted psychotherapy in 10 people with chronic, treatment-resistant posttraumatic stress disorder (PTSD). The study will include an open-label lead-in in two subjects followed by a randomized, double-blind arm comparing 125 vs. 25 mg MDMA in eight participants, and an open-label arm for participants who received active placebo. This study is also intended to continue the development of a manualized psychotherapeutic approach to this potential treatment, to be used in the planning of possible Phase 3 studies.

### **2.2 Background**

#### **2.2.1 Post Traumatic Stress Disorder (PTSD)**

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 U.S. general population is between 6 and 10% [3-7], but it is common in other countries as well [4, 8-11]. According to some estimates, PTSD appears to be less prevalent in the general population of Europe at 1.9% [12]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [13], and it is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [14]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [15-17].

The search for novel and more effective treatments is of major public health and economic significance. PTSD is typically a chronic illness [3, 18] associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [4-7]. People with PTSD face challenges in relationships and work productivity [19]. In the U.S. 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 a third of the patients still had symptoms several times per week after 10 years [3]. Forty to sixty percent of PTSD patients were found to be resistant to treatment in this study. In a comparison of two types of psychotherapy for women with PTSD after sexual assault in 2002, 47% of each treatment group was diagnosed with PTSD based on high Clinician Administered PTSD Scale (CAPS) scores [20].

Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [21]. PTSD treatment goals include alleviating symptoms and correcting stress-induced neurochemical abnormalities associated with the condition. Two selective serotonin reuptake inhibitors (SSRI), sertraline and paroxetine, are currently marketed as PTSD medications in the U.S. These drugs are known to affect the serotonergic components of PTSD, but it is not known whether they can arrest and reverse the hippocampal atrophy found in individuals with PTSD [34]. In addition, SSRIs affect PTSD symptoms in a dosage dependent manner and they must be used every day in order to be effective [22].

Another treatment approach is to develop drugs and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal associated with 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 proven to be effective in treating some symptoms of PTSD [28], although some patients may need more than one treatment to reduce or resolve those symptoms [20]. A recent meta-analysis concluded that all “bona fide” psychotherapies, including those listed above, are similarly effective with PTSD [29].

At least a third of PTSD patients fail to respond to established PTSD psychotherapies or respond in a way that falls outside of clinical significance [23-25]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [26], and another randomized, double-blind study found no difference between sertraline and placebo in the treatment of PTSD [27]. 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 (see [28] for a review). Examples of this are virtual reality-assisted exposure therapy [29, 30] and D-cycloserine-assisted psychotherapy [31]. MDMA-assisted psychotherapy is another example of such emergent treatments.

### **2.2.2 MDMA**

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the psychedelic drug mescaline. It was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s [32, 33]. In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was placed in Schedule 1 in 1985 as a result of extensive non-medical use [34-36]. Placement in Schedule 1 prohibited it for use except in a federally approved research setting.

Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [37-40]. Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can “reduce or somehow eliminate fear of a perceived threat to one’s emotional integrity” [38]. Elimination of these “conditioned fear responses” can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience [38]. Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens [41]. The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others.

### **2.2.3 Previous Clinical Experience with MDMA**

Classification as a Schedule 1 drug hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and efficacy of MDMA-assisted



psychotherapy has become more feasible [1, 42, 43]. The first double-blind, placebo controlled U.S. Phase 1 study sanctioned by the FDA was conducted in 1994, with findings that suggested MDMA caused a significant increase in body temperature and heart rate in some healthy volunteers [44]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting [44]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [45].

The potentially therapeutic effects of MDMA were initially investigated starting in 2000 in a MAPS-sponsored dose-response pilot study in Spain in women survivors of sexual assault with treatment-resistant PTSD [46, 47]. Unfortunately, the study in Spain was halted in 2002 due to political pressure from the Madrid Anti-Drug Authority. Prior to its suspension, six women were enrolled and treated in this study without any adverse events or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 to 75 mg [47].

As of 2010, MDMA has been administered to approximately 494 research participants, in both Phase 1 and Phase 2 studies, without any occurrences of drug-related Serious Adverse Events (SAEs) [48-62]. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [34].

MAPS recently completed its first U.S. study of MDMA-assisted psychotherapy for the treatment of PTSD, known as MP-1. This study employed the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded independent rater at baseline, 3 to 5 days after each experimental (MDMA or placebo) session, and two months after the final experimental session. All participants in this study tolerated MDMA, and MP-1 data suggests that MDMA is associated with significantly greater improvement in PTSD than placebo [2]. Findings from the long-term follow-up evaluating the US subjects at an average of 40 months post-treatment, suggests that the therapeutic benefits have been sustained over time [63]. The sponsor has also supported a randomized, double-blind study of MDMA-assisted psychotherapy in twelve subjects with PTSD in Switzerland (data analysis in process), and in five subjects in our initial Israeli MDMA/PTSD pilot study (data summarized in our abbreviated report).

#### **2.2.4 MDMA-assisted Psychotherapy for PTSD**

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]. In contrast to daily administrations of SSRIs, this treatment consists of several sessions of MDMA-assisted psychotherapy within the context of a moderate course of non-drug psychotherapy.

Treatment goals of MDMA-assisted psychotherapy for PTSD include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. Reports of past experience with MDMA-assisted psychotherapy suggest that it may also counteract the effects of PTSD. In fact, the biologic and psychotherapeutic approaches overlap and 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 [64]. 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 [65, 66].

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.

### **2.3 Protocol Purpose**

This Phase 2 study is a randomized, double-blind study in 10 subjects comparing the effects of low and full dose MDMA as an adjunct to manualized psychotherapy. The first two subjects will be enrolled in the open label full dose lead-in. The remaining eight subjects will enroll in Stage 1 of the protocol and receive either an active placebo dose (low dose) or a fully active dose of MDMA during two experimental psychotherapy sessions, each lasting six to eight hours and scheduled three to five weeks apart. Five subjects will be randomized to the full dose and 3 subjects will be randomized to the active placebo dose of MDMA. The extent of PTSD symptoms will be assessed at baseline, and two months after the second experimental session by a clinician and throughout using a self-report measure. Subjects enrolled in Stage 1 who receive the active placebo will have the opportunity to enroll in Stage 2 of the protocol and complete open-label experimental sessions with the fully active dose of MDMA on the same schedule as Stage 1. Participants assigned to receive the full dose of MDMA will be assessed at 12 months after the second experimental session of Stage 1, and participants assigned to active placebo who enroll in Stage 2 will be assessed 12 months after the second Stage 2 experimental session. This study will allow comparison between the impact of active placebo and full dose MDMA on PTSD symptoms, and on symptoms of depression and sleep quality. This study will also permit the refinement of the treatment manual.

### **2.4 Rationale of Dose Selection**

This study will compare the effects of psychotherapy sessions assisted by full or active placebo dose MDMA. Active placebo will be 25 mg MDMA followed one and a half to two and a half hours later by 12.5 mg, and the fully active dose will be 125 mg followed one and a half to two and a half hours by 62.5 mg.

**Table 1. Dose Regimen**

	<b>Initial Dose</b>	<b>Supplemental Dose</b>	<b>Cumulative Dose</b>
<b>Active Placebo Dose</b>	25 mg	12.5 mg	37.5 mg
<b>Full Dose</b>	125 mg	62.5 mg	187.5 mg

The full MDMA dose to be used in this study is identical to those used in previous studies in the U.S., Switzerland and Israel. Previous researchers have also used doses within this range [44, 45, 49, 56, 67, 68] [49, 67, 69-72]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [34, 36, 39]. The initial full dose is expected to produce all the commonly reported effects of MDMA. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose.

The active placebo dose of MDMA was chosen on the basis of its demonstrated ability to produce detectable subjective effects in the absence of full therapeutic effects, thus serving as an active placebo [45, 70, 73]. These doses are expected to produce increases in positive mood and tension, but without the range of effects seen at higher doses. This dose was also used in the previous Swiss and Israeli studies conducted by the Sponsor.

### **3.0 Protocol Objectives**

The objective of this study is to examine whether a full dose of MDMA versus an active placebo dose of MDMA used in conjunction with psychotherapy will reduce or attenuate PTSD symptoms and to collect safety data.

#### **3.1 Primary Objective**

1. Assess changes in PTSD symptoms in participants receiving the full dose of MDMA and the active placebo dose as measured via CAPS score at baseline and the end of Stage 1.

#### **3.2 Secondary Objectives**

- Assess changes in self-reported PTSD symptoms in participants receiving the full dose of MDMA and the active placebo dose as measured via PDS score at baseline, during the third integrative session after each experimental session and at the end of Stage 1.
- Assess depression symptoms via the Beck Depression Inventory- II (BDI-II) at baseline and the end of Stage 1.
- Assess quality of life via the Global Assessment of Functionality (GAF) at baseline and the end of Stage 1.

- Assess self-reported sleep quality via the Pittsburgh Sleep Quality Index (PSQI) at baseline and the end of Stage 1.
- Assess PTSD symptoms via CAPS, depression symptoms via BDI-II, quality of life via GAF and sleep quality with PSQI at the end of Stage 2 in all participants enrolled in Stage 2.
- Assess long-term effects symptoms of PTSD, depression and global function via CAPS, BDI-II and GAF one year after the final MDMA-assisted psychotherapy session for each participant.
- Assess changes in PTSD symptoms via PDS during the third integrative session after each Stage 2 experimental session and at the end of Stage 2.

### **3.3 Safety Objectives**

The safety objectives of the study are to monitor and assure safety of subjects during and after the experimental sessions by assessing physiological effects, psychological distress, adverse events, spontaneously reported reactions 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, with comparisons made between subjects in each condition.
- Subjective Units of Distress (SUD) scores and vital signs including blood pressure, heart rate and temperature will be measured during each experimental session, and results will be compared between groups.
- Serious adverse events, adverse events and spontaneously reported adverse events (“reactions”) will be collected during the study according to Section 8.5.

### **4.0 Protocol Design**

This randomized, double-blind, active placebo controlled study will examine the safety and efficacy of MDMA-assisted psychotherapy in subjects diagnosed with chronic, treatment-resistant PTSD of at least six months duration. The open-label lead-in, Stage 1 and Stage 2 will follow the same basic sequence of events and methods. The schedule will include two MDMA-assisted psychotherapy sessions scheduled approximately one month apart with a male/female co-therapist team. There will be three sets of male/female co-therapist teams. Subjects will remain with only one team for the entirety of the study. The first two teams will complete treatment of one of the two lead-in subjects for training purposes. Upon enrollment, subjects will meet with their therapist team for 3 preparatory sessions. Each MDMA-assisted psychotherapy session 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. Experimental sessions will be followed by two additional integrative sessions. PTSD symptoms will be assessed throughout Stage 1. For subjects continuing on to Stage 2, PTSD symptoms will be assessed throughout Stage 2. All subjects will be evaluated for long-term effects 12 months after their last experimental session. (See Table 3 Time and Events).

The open-label lead-in will follow the same sequence of events as Stage 1 and will enroll the first two subjects. The Sponsor will conduct an ongoing review of videotapes of at least two of four experimental sessions, entry criteria, vital signs and reaction data for completed sessions and any adverse events (AEs). Stage 1 will proceed after the data has been reviewed by the Sponsor and feedback provided to the co-therapist teams to ensure proper therapist training and subject safety. After review, the Sponsor will notify the site when Stage 1 may proceed. The goal of the lead-in will be to ensure standardization of therapy techniques in the Sponsor's ongoing effort to manualize MDMA-assisted psychotherapy.

In Stage 1, subjects will be randomly assigned to receive two experimental psychotherapy sessions assisted by either active placebo MDMA (3 subjects) or full dose MDMA (5 subjects). Subjects who receive the active placebo dose of MDMA will be offered the option to enroll in the open-label Stage 2 unless they meet any exclusion criteria for study participation. In Stage 2, subjects will receive full dose MDMA and the experimental sessions will otherwise follow the same sequence of events after a single preparatory session. (See Table 3 Time and Events)

All outcome measures will be assessed by a blinded independent rater. The independent rater will assess PTSD symptoms with the CAPS and PDS, quality of life with the GAF, symptoms of depression with the BDI-II, and sleep quality with the PSQI. The subjects will complete the PDS, a self-report measure of their PTSD symptoms, to provide correlations with measures administered by the independent rater. The PDS will be completed at baseline, during every third integrative session after an experimental session, and at the end of each Stage. Baseline assessments will be compared with assessments made in Stage 1.

All subjects will complete a follow-up occurring 2 months after their last experimental session in Stage 1 and Stage 2, if applicable. The blind will be broken for all subjects in Stage 1 after completing this assessment. In addition all subjects will complete a visit 12 months after their final experimental session where outcome measures and a questionnaire on any lasting benefits or harms of the treatment will be administered.

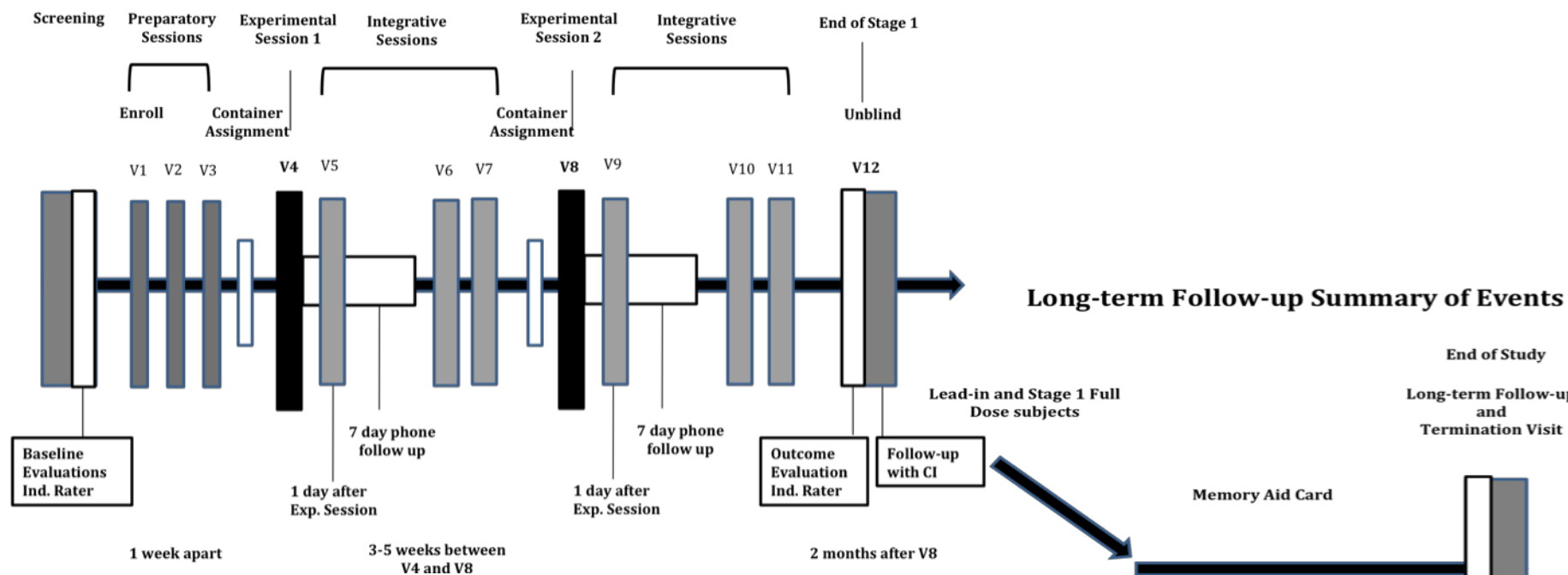
At each visit with the therapists, the subject's general wellbeing and suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS). Adverse Events and Concomitant Medications will be collected as described in Section 8.5 and 9.0 of the protocol.

#### **4.1 Planned Duration of Study**

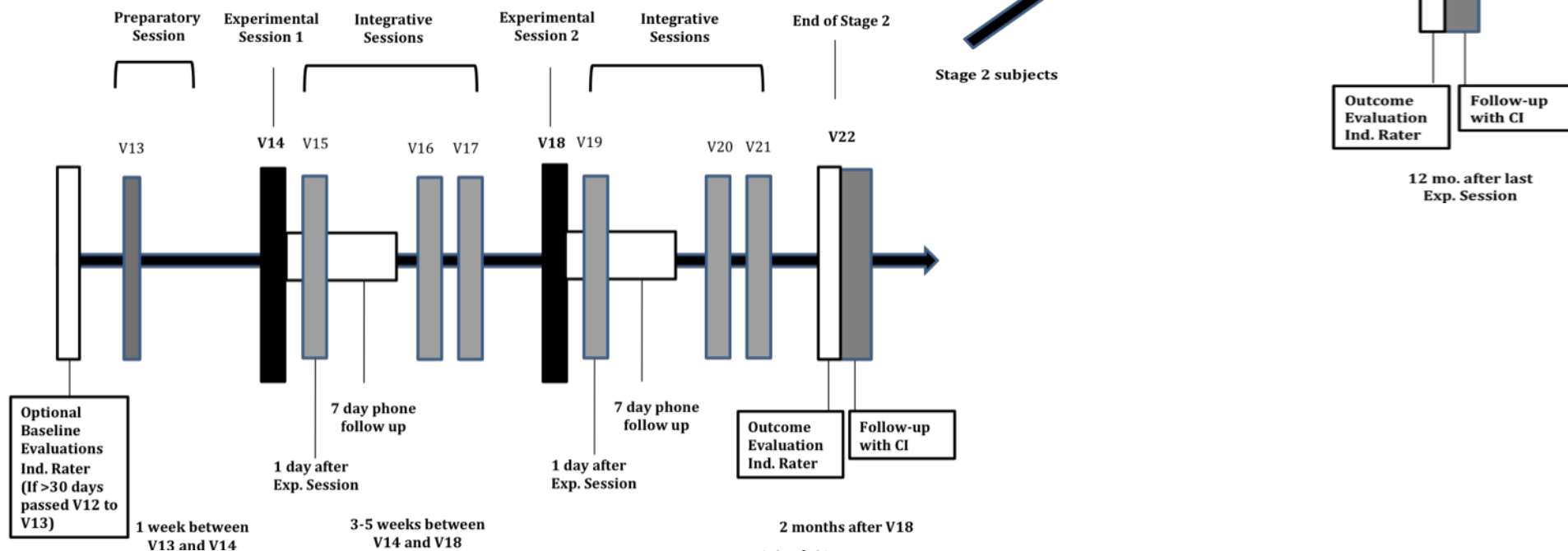
Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include screening and the follow-up portion of the study.

- Open-label lead-in and Stage 1 only subjects: 14 months
- Stage 1 subjects who continue to Stage 2: 18 months

## Stage 1 Summary of Events



## Stage 2 Summary of Events



<b>Table 2. Time &amp; Events MP9 Stage 1</b>	<b>Screen/Baseline</b>	<b>Preparatory</b>	<b>Experimental Session 1</b>		<b>Experimental Session 2</b>		<b>End of Stage 1</b>
Visit #	Prior to Enrollment	V1, 2, 3	V4	V5, 6, 7	V8	V9, 10, 11	V12
Type of Visit	Baseline Screening may take place over more than one day up to one month prior to Visit 1	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Follow-Up & Outcome
Visit Timing or Study day or Window		Approx. 1 week apart	3-5 weeks post V1	Approx. 1 week apart <sup>A</sup>	3-5 weeks post V4	Approx. 1 week apart <sup>A</sup>	May happen over more than 1 day. 2 months post V8
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
Medication Taper (if applicable)		X					
Drug Screen	X		X		X		
Pregnancy Screen (if applicable)	X		X		X		
CAPS, GAF, BDI –II, PSQI (with Ind. Rater)	X						X
Study Enrollment after meeting I/E		X <sup>B</sup>					
Record to Audio/Video		X	X	X	X	X	
General Well-Being		X	X <sup>D</sup>	X	X <sup>D</sup>	X	X
Obtain Container Assignment from Randomization Program			X <sup>C</sup>		X <sup>C</sup>		
C-SSRS	X	X <sup>H</sup>	X <sup>D, E, F</sup>	X <sup>J</sup>	X <sup>D, E, F</sup>	X <sup>J</sup>	X
Administer IP Drug + Therapy			X		X		
Monitoring of BP, Pulse and Temp.			X		X		
SUD			X <sup>E, G</sup>		X <sup>E, G</sup>		
Beliefs of Condition Assignment				X <sup>I</sup>		X <sup>I</sup>	
Overnight Stay			X		X		
PDS	X			X <sup>N</sup>		X <sup>N</sup>	X
Integrative Therapy Session				X		X	
7 days Integrative Telephone Contact				X <sup>J</sup>		X <sup>J</sup>	
AEs Requiring Medical Attention			X	X	X	X	X
Spont. Reactions and all AEs			X <sup>K</sup>	X <sup>K</sup>	X <sup>K</sup>	X <sup>K</sup>	
AEs related to changes in psychiatric status or withdrawal		X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X
Unblinding							X <sup>L</sup>
RRPQ							X <sup>M</sup>
Issue Memory Aid Card							X <sup>M</sup>

A =First Integrative session is 1 day after Exp. session B =Only on Visit 1 C = At least 24 hrs prior to exp. session D =Approximately 6 hours post MDMA E =At the beginning of the session F =As needed G =Approximately every 60 minutes H =Given on 2nd preparatory session only (V2) I= At 1<sup>st</sup> integrative visit after each Exp. Session for subjects & therapists and at V12 for the independent rater J = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days K= Spontaneously reported reactions will be collected on the day of MDMA administration and for seven days after each Exp. Session. L= Determine after completion: Go on to Long-term follow up or Stage 2 M= Only for subjects not going to Stage 2 N= Subjects will complete PDS on third integrative session only

<b>Table 3. Time &amp; Events MP9 Stage 2</b>	<b>Preparatory</b>	<b>Experimental Session 1</b>		<b>Experimental Session 2</b>		<b>End of Stage 2</b>	<b>Long Term Follow up after Stage 1 or Stage 2</b>	<b>Long Term Follow-Up</b>
Visit #	V13*	V14	V 15, 16, 17	V18	V 19, 20, 21	V22		1 Year Follow-up
Type of Visit	Preparatory Session	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Follow-Up & Outcome		Follow-Up & Outcome
Visit Timing or Study day or Window	Within 1 month of V12*	1 week post V13	Approx. 1 week apart <sup>A</sup>	3-5 weeks post V14	Approx. 1 week apart <sup>A</sup>	May happen over more than 1 day. 2 months post V17		May happen over more than 1 day. One Year After V8 or V17
Confirm Informed Consent	X							
Confirm Inclusion/Exclusion	X							
Entry into Stage 2	X							
Collect Concomitant Medication	X	X	X	X	X	X		X
Record to Audio/Video	X	X	X	X	X			
General Well-Being	X	X <sup>B</sup>	X	X <sup>B</sup>	X	X		X
Drug Screen		X		X				
Pregnancy Screen (if applicable)		X		X				
CAPS, GAF, PSQI, BDI-II (with Ind. Rater)	Use V12*					X		X
C-SSRS	X	X <sup>B, C, D</sup>	X	X <sup>B, C, D</sup>	X	X		X
Administer IP Drug + Therapy		X		X				
Monitoring of BP, Pulse and Temp.		X		X				
SUD		X <sup>C, E</sup>		X <sup>C, E</sup>				
Overnight Stay		X		X				
PDS	Use V12*		X <sup>H</sup>		X <sup>H</sup>	X		X
Integrative Therapy Session			X		X			
7 days Integrative Telephone Contact			X <sup>F</sup>		X <sup>F</sup>			
AEs Requiring Medical Attention	X	X	X	X	X	X		
Spont. Reactions and all AEs		X <sup>G</sup>	X <sup>G</sup>	X <sup>G</sup>	X <sup>G</sup>			
AEs related to changes in psychiatric status or withdrawal	X	X	X	X	X	X		X
Serious Adverse Events	X	X	X	X	X	X		X
RRPQ						X		
Issue Memory Aid Card						X		
Follow up Questionnaire								X
Termination Visit								X

\* Re-baseline if Visit 13 is more than 1 month from V12, then the measures from V12 will need to be repeated prior to starting Stage 2.

A = First Integrative session is 1 day after Exp. session B = Approximately 6 hours post MDMA C = At the beginning of the session D = As needed E = Approximately every 60 minutes F = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days G = Spontaneously reported reactions will be collected on the day of MDMA administration and for seven days after each Exp. Session. H = Subjects will complete PDS on third integrative session only



## **4.2 Recruitment and Subject Population**

Participants may be men or women aged 18 or older with a confirmed diagnosis of chronic PTSD who have undergone at least one treatment for PTSD without achieving remission. Prior treatment can include psychotherapeutic or pharmacological treatments, and people who have undergone one or more prior treatments are eligible for study participation. Subjects would not be excluded for having more than one traumatic event. Subjects must have a CAPS score equal to or greater than 50 and must meet all inclusion criteria and no exclusion criteria at baseline. Participants must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA. Participants will be recruited through printed ads, internet ads, referrals from other psychiatrists, psychotherapists or physicians, through the Israeli Defense Forces (IDF) and through word of mouth. The first ten participants who meet all inclusion criteria without meeting any exclusion criteria will be admitted to the study. All recruitment materials and advertisements will be approved by the institution's IRB/EC.

### **4.2.1 Inclusion Criteria**

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

1. Meet DSM IV criteria for chronic PTSD with a duration of at least six months. Participants may have experienced one or more traumatic event;
2. Have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms;
3. Have had at least one unsuccessful attempt at treatment for PTSD:
  - 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. May have a concurrent affective disorder, excepting bipolar affective disorder 1;
5. Are at least 18 years old;
6. If in ongoing psychotherapy at the time of recruitment, are able to continue to see their outside therapist during the course of the study. Subjects must sign a release permitting the investigators to communicate directly with their therapist.
7. May not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session at the end of Stage 1 or 2, as applicable;
8. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician.
9. Agree to, for one week preceding each experimental 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;
10. Agree to take nothing by mouth except alcohol-free liquids after 24:00 (midnight) the evening before the experimental session;
  11. Agree to refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session;
  12. Agree not to use caffeine or nicotine for 1 hour before and 3 hours after ingesting the drug, or until the therapists deem it safe to do so;
  13. Are willing to commit to medication dosing, experimental sessions, follow-up sessions and to complete evaluation instruments;
  14. Are willing to remain overnight at the study site after each experimental session until after the integrative session occurring the next morning;
  15. Are willing to be driven home the morning after the experimental sessions, after the integrative therapy session either by a driver arranged by the subject or by the site personnel or taxi;
  16. Are willing to be contacted via telephone on a daily basis by one of the therapists for a week after each experimental session;
  17. Are willing to refrain from participating in any other clinical trial for the duration of this clinical trial, including the follow up period;
  18. If female subjects of childbearing potential, must have negative pregnancy test results, be willing to have pregnancy tests and must agree to use an effective form of birth control;
  19. Are proficient in speaking and reading Hebrew;
  20. Agree to have all psychotherapy sessions recorded to audio/video.

#### **4.2.2 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;
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;
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, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration (Subjects with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded);

5. Have hypertension using the standard criteria of the American Heart Association (values of 140/90 or higher assessed on three separate occasions [74]);
6. Have liver disease;
7. Have history of Diabetes Type I or II;
8. Have history of hyponatremia or hyperthermia;
9. Weigh less than 48 kg;
10. Would present a serious suicide risk or who are likely to require hospitalization during the course of the study;
11. Have used “Ecstasy” (material represented as containing MDMA) more than five times or at least once within 6 months of the MDMA session;
12. Require ongoing concomitant therapy with a psychiatric drug, including SSRIs, SNRIs, or MAOIs;
13. Meet DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days;
14. Have glaucoma, significant atherosclerosis or hyperthyroidism;
15. Have any current problem, which in the opinion of the investigator or medical monitor, might interfere with participation in the study;
16. Are not able to give adequate informed consent.

## **5.0 Methods**

### **5.1 Measures**

The following outcome and safety measures will be used in Stage 1 and Stage 2:

#### **5.1.1 Outcome Measures**

The primary outcome measure will be the CAPS, a clinician-scored measure for PTSD diagnosis and measure of symptom intensity and severity. A qualified, blinded independent rater will perform the CAPS. The independent rater will not be present during the subject’s 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 subject’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 interview takes approximately one hour to complete. The CAPS has been determined to have good internal consistency, concurrent validity, and test/retest reliability [75, 76]. An independent rater will assess all subjects at baseline and the end of Stage 1. The independent rater will also assess applicable subjects at the end of Stage 2 and 12 months after the subject’s final experimental session.

The secondary measure of PTSD symptoms will be the PDS, a self-report measure designed to follow DSM IV criteria for assessing PTSD. The measure is derived from the Posttraumatic Symptom Scale – Self Report (PSS-SR), a measure also intended to tap into diagnostic criteria for PTSD. The PDS contains 49 items, with responses made on a

four-point scale, ranging from 0 (“not at all”) to 3 (“five or more times a week”). The PDS consists of a list of 12 potential traumatic events, 12 items addressing elements of the traumatic event, of 17 symptom items, and nine items assessing impact on areas of life function [77]. Items addressing elements of the traumatic event and life function are answered as either present or not present (Yes or No). The seventeen items are summed to create a symptom severity scale. Cronbach’s alpha for the symptom severity scale is 0.92. The PDS has test-retest reliability of 0.74 after a two-week and one-month interval, and subscales are inter-correlated, with correlations ranging from 0.73 to 0.82, and PDS scores had a moderate to good correlation with SCID diagnosis, with kappa = 0.65 [77]. The Hebrew translation of the 17-item symptom scale of the PDS will be used for this study [78, 79]. A study of the reliability and validity of the Hebrew translation has been conducted [80], with at least one report giving internal consistency of 0.94 [81].

The Beck Depression Inventory-II (BDI-II) is a 1996 revision of the BDI, a 21-item self-report measure [82, 83], that will serve as a measure of depression according to DSM-IV criteria[84]. The BDI-II has been validated, has high internal consistency and good test/re-test reliability and is not overly sensitive to daily variations in mood. It takes five to ten minutes to complete [84]. Score cutoffs indicate: 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression. Higher scores indicate more severe depressive symptoms. The BDI-II has been translated and validated in Hebrew [85]. Subjects will complete the BDI-II at the same times as the CAPS.

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 GAF is a reliable, validated measure of social functioning [86]. Subjects will complete the GAF at the same time as the CAPS.

The Pittsburgh Sleep Quality Index (PSQI) is a measure of self-reported sleep quality over a one month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. It consists of 19 items, with possible responses ranging from zero to 4 on a five-point scale [87]. The PSQI consists of seven sub-scales; sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. These are all summed to produce a single global scale. Global scores can range from 0 to 21, with higher scores reflecting poorer sleep quality, and a score below 5 indicative of good sleep. It takes five to ten minutes to complete. Test-retest reliability ranges from 0.85 to 0.87, and it is internally consistent, with a Cronbach’s alpha of 0.83[87, 88]. Global scores correlate with other measures of alertness and self-reported sleep quality [89]. The Hebrew translation will be used [90]. Analysis of the Hebrew translation found that it has a Cronbach’s alpha of 0.70 in sleep clinic patients and 0.52 for non-clinic patients, with the lower alpha possibly the result of sleep clinic patients referred for snoring rather than insomnia.

The Reactions to Research Participation Questionnaire (RRPQ) [91] 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 long-term follow up questionnaire has been developed internally by the Sponsor to assess long-term benefits and harms of MDMA-assisted psychotherapy at the 12 month follow up visit. It will be translated into Hebrew.

All psychotherapy sessions, including experimental sessions, will be recorded to audio and video, with all recordings preserved for research purposes. Safety measures will be applied as described below to minimize risks associated with drug-assisted psychotherapy sessions.

### **5.1.2 Safety Measures**

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

The C-SSRS (Hebrew translation) is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [92]. 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. Suicidality will be assessed at baseline, once during any face-to-face visit, during the second and seventh days of telephone contact, and twice during each experimental session. Subjects who are discontinuing medication to participate in the study will complete the C-SSRS before and after medication washout. The C-SSRS data will be collected on Case Report Forms (CRFs) for all administrations except for the second integrative session, unless an increase in suicidality is observed by the therapists. C-SSRS data from the second integrative session after each experimental session will be kept with the subject's source record.

The therapists will assess general wellbeing during each preparatory 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. Blood pressure will also be measured more frequently if there are symptoms, such as chest pain, shortness of breath or neurological symptoms,

that may be indicative of hypertension. The therapists will measure subject body temperature approximately every 60 to 90 minutes. Cardiovascular effects will be assessed via blood pressure measurement. The timing of these measurements will be adjusted so they do not interfere with the therapeutic process.

All AEs and spontaneously reported reactions will be collected as described in section 8.5. Adverse events and spontaneously reported reactions may be collected during face to face visits or over the telephone. Commonly reported reactions that are spontaneously reported are collected for seven days after each experimental session on a separate CRF page and will be categorized as mild, moderate or severe.

## **5.2 Study Procedures and Visit Descriptions**

### **5.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study)**

All individuals who enter screening, as defined in this section, should be assigned a screening number and recorded on the “subject screening log” where information on the selection of potential subjects in the trial should be collected. The subject screening number should also be recorded on the subject’s informed consent form. If a subject is enrolled, the study staff should record the enrollment date and assign a subject number. If a subject is not enrolled, an explanation should be recorded on the screening log. A CRF will not be completed for subjects who are not enrolled. These subjects will only be documented on the screening log and source records. It is the responsibility of the investigator to file the screening log in the investigator site file (ISF) to be readily available for on-site monitoring and/or inspection by relevant authorities. Screening may take place over more than one day and up to one month prior to Visit 1. If, after reviewing all information, the investigator concludes that a subject is eligible, he will enroll the subject in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

- a. Explain and obtain written informed consent from the subject. Written informed consent must be obtained prior to performing any tests or evaluations for the study.
- b. Assign the subject a screening number. Complete the screening log.
- c. Subjects will provide a medical and psychological history.
- d. Review the ability of females of childbearing potential to become pregnant and their commitment to practice appropriate birth control as determined by the investigator for the total duration of the study.
- e. A physician will perform a general physical examination. 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
- Human Immunodeficiency Virus (HIV) serology
- Urine-dip pregnancy test on females with childbearing potential
- C-SSRS to assess suicide risk

Results of HIV serology will be kept confidential, and appropriate referral for counseling will be made if necessary. The clinical laboratory values will be used to establish eligibility and will be kept with the subject's source record. The clinical laboratory values will not be captured in the CRF, but will be used to establish eligibility and will be kept with the subject's source record. Clinically significant abnormal values will be captured as medical history. If, upon examination, there are questions raised about possible medical problems, the therapists will request a review of subject medical records and request additional tests or assessments as indicated.

An independent rater who will not be present during any of the therapy sessions will administer:

- SCID to assess eligibility
- CAPS to assess PTSD symptoms
- PDS to assess self-reported PTSD symptoms
- BDI-II to assess depression symptoms
- GAF to assess general psychological function
- PSQI to assess sleep quality

### **5.2.2 Preparatory Psychotherapy Sessions (Visits 1, 2 and 3)**

Subjects who do not complete all screening activities will not be enrolled. If all inclusion criteria and no exclusion criteria are met, eligibility will be confirmed with the subject during Visit 1. After eligibility is confirmed, the subject will be enrolled during Visit 1 and issued a subject number. The first preparatory session will take place after enrollment during Visit 1. Remaining preparatory sessions will be scheduled as described in the Time and Events table.

Upon enrollment, subjects who must refrain from taking a psychiatric medication will begin tapering off that medication following a time course appropriate for the medication given its half-life, with the first experimental session scheduled to occur after complete washout. The therapists 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.

- a. Record preparatory sessions to audio and video. Subjects may receive

- copies of audio or video recordings from these preparatory sessions upon request.
- b. AEs and Medications will be recorded as described in Section 8.5 and 9.0 of the protocol from the time the subject is enrolled at Visit 1.
  - c. The therapists will inquire about any possible changes in the subject's health to ensure that subject continues to meet eligibility criteria and if applicable, will confirm that the subject has appropriately tapered off of medications.
  - d. The subject will undergo three preparatory sessions lasting at least an hour with the therapists, who will be a male and a female co-therapist team. The therapists will work with the subject to prepare him or her for MDMA-assisted psychotherapy. The therapists and subject will seek to form a strong working relationship with each other, and they will help the subject prepare for upcoming experimental sessions. Preparatory sessions will promote a safe space for confronting trauma-related memories, emotions and thoughts. Subjects will remain with the therapist team they begin with throughout the study.
  - e. The subject and therapists will discuss goals for the experimental session and will review what will happen during the experimental session, following standard procedures and techniques discussed in the Sponsor's treatment manual.
  - f. During one of the preparatory sessions the therapists will introduce the subject to the attendant that will remain with the subject during each overnight stay after each MDMA-assisted psychotherapy session. The attendant will be an individual with previous training in managing psychological distress.
  - g. If a subject would like another individual present during or after the experimental session, a meeting between the therapists and that individual will be scheduled prior to the first experimental session. There must be mutual agreement between the subject and therapists concerning the presence of the support individual.
  - h. Subjects will complete the C-SSRS just prior to beginning the second preparatory session, unless a subject is still undergoing medication washout. Subjects still undergoing medication washout will complete the C-SSRS during the second preparatory session or at a point after washout is complete.
  - i. General wellbeing will be assessed at each preparatory session.
  - j. AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.
  - k. During the third and last preparatory session, the therapists will give the Subject Information Sheet to the subject, which includes instructions and restrictions for conduct 24 hours prior to receiving the drug, 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 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 experimental session.
    - Subjects must not use caffeine or nicotine for 1 hour before and 3 hours after ingesting the drug, or until therapists deem it safe to do so.
    - Subjects must refrain from smoking marijuana for at least 3 days prior to the experimental session. They may smoke marijuana on the 8<sup>th</sup> day after the experimental session if needed. This will be collected with the Concomitant Medications.



### 5.2.3 Experimental Sessions (Visit 4 and 8)

Subjects in Stage 1 will receive two double-blind experimental sessions of MDMA-assisted psychotherapy scheduled approximately 3-5 weeks apart, and subjects in the open label lead-in and open label Stage 2 will receive two experimental sessions with the full dose of MDMA. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions, and all procedures except the drug received will be the same.

- a. At least 24 hours prior to the first experimental session the subject will be randomized. The therapist team conducting the session will obtain the container assignment using a web-based randomization program prior to the session.
- b. On the day of the experimental session, the subject will arrive approximately 1-1.5 hours prior to drug administration.
- c. Confirm continuing eligibility by reviewing inclusion/exclusion criteria.
- d. Perform a urine drug screen. 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.
- e. If a woman is of childbearing potential, perform a urine pregnancy test. A positive pregnancy screen is cause for withdrawal from the protocol.
- f. If the subject continues to meet criteria and the subject reports that he/she followed appropriate rules and restrictions, the session will proceed.
- g. Review procedures for the experimental session with the subject.
- h. Record the entire session to video and audio. Subjects may receive a copy of audio or video recordings of their experimental sessions upon request.
- i. The session will last for approximately eight hours or longer, followed by an overnight stay at the study site.
- j. The subject will complete the C-SSRS approximately one hour to a half hour prior to drug administration.

**Table 4. Schedule of procedures and measures for experimental sessions.**

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	2 <sup>nd</sup> Baseline BP, Pulse, Body Temperature (BT), SUD
10:00	<b>MDMA Administration</b> , begin recording to audio and video
10:30	BP, Pulse
11:00	BP, Pulse, SUD, BT
11:30	BP, Pulse; <b>Can administer optional supplemental dose</b>
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, BT
Approximately 6 hours after drug administration	C-SSRS, General Wellbeing

- k. Before drug administration, discuss and review the subject's goals, intentions and concerns and some of the commonly experienced effects of MDMA.
- l. Instruct the subject not to use caffeine or nicotine 1 hour before or 3 hours after the dose of drug.
- m. Subject body temperature will be measured 15 and 5 minutes prior to initial dose administration and approximately every hour after that. The therapists may make more frequent measurements if body temperature exceeds more than 1°C above baseline.
- n. Subjects will complete the SUD 15 and 5 minutes prior to initial dose administration. 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 therapists can make a greater number of measurements as their clinical judgment dictates.
- o. Measure blood pressure and pulse 15 and 5 minutes prior the experimental session, and once every half-hour throughout the experimental session if the established thresholds for normal blood pressure and pulse have not been exceeded 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. Measurements should be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. The therapists may also make more frequent measurements if a subject exhibits symptoms indicative of hypertension.
- p. At approximately 10:00 in the morning, subjects will receive the initial dose of drug along with a glass of water.
- q. The subject will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided if the subject wishes to use them. Subjects will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material [77-79]. Subjects may speak to the therapists whenever they wish, who will provide guidance and support as needed.
- r. After the first hour, if the subject has not spoken spontaneously, check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapists will support and encourage the subject in emotional processing and resolution of whatever psychological material is emerging.
- s. Record any spontaneously reported reactions during the session.
- t. Provide water and electrolyte containing fluids throughout the session but not to exceed 3 L overall.

- u. 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 therapists and subject.
- v. Provide food during the latter part of the session.
- w. If there is a support-individual who has previously been asked and has agreed to be present during part or all of the MDMA session, that person may arrive during the session at whatever time has been agreed upon, but will wait in the waiting room until brought back to the session room by one of the therapists. The support person may arrive after the session has ended.
- x. If it is appropriate to do so, 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.
- y. End the session if all medical and psychiatric parameters are acceptable and the subject is alert, ambulatory and emotionally stable.
- z. The therapists will depart the site when they have concluded that the subject is emotionally and medically stable. Therapists shall remain available to subjects during the experimental session and for one week after via 24-hour cellular phone.
- aa. Spontaneously reported reactions, AEs and Medications will be collected as described in Sections 8.5 and 9.0 of the protocol.

Subjects will remain overnight in an appropriately furnished room at the study site. With the approval of the therapists, a companion may accompany the subject during the overnight stay. An 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 therapists. The subject and a companion (if applicable) will receive information that will allow them to contact the therapists 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.

#### **5.2.4 Integrative Sessions 24 Hours after Experimental Session (Visits 5 and 9)**

- a. On the morning after each experimental session, both of the therapists from the subject's team will meet with the subject during a 90-minute integrative therapy session.
- b. The entire integrative psychotherapy session will be recorded to audio and video. Subjects may receive copies of this session upon request.
- c. Subjects will complete the C-SSRS just prior to beginning each integrative session.
- d. Prior to integrative psychotherapy, the subject and both therapists will indicate their beliefs concerning subject condition assignment.
- e. Discuss and review events that occurred with the subject during the integrative session, including thoughts, feelings and memories. If necessary, the therapists will help the subject to reduce any residual psychological distress he or she is

- experiencing. The therapists will also encourage the transfer of states of acceptance, feelings of intimacy, closeness and reduced fear experienced in experimental sessions to emotionally threatening everyday situations. The therapists will be supportive, validating the experience and facilitating understanding and emotional clearing.
- f. The therapists will remain accessible any time the subject needs support outside the scheduled integration sessions.
  - g. Assess the subject's mental health and the presence of any remaining reactions during integrative psychotherapy immediately after each experimental session.
  - h. Integrative psychotherapy sessions can also serve as an opportunity for the therapists to gather information about the effects of the drug on the subject in an unstructured manner.
  - i. After the integrative psychotherapy sessions, a person previously selected by the subject will provide a ride home to the subject. 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 therapists will assist the subject in finding an alternative means of returning home.
  - j. Spontaneously reported reactions, Adverse Events and Medications will be collected as described in Sections 8.5 and 9.0 of the protocol.
  - k. Remind the subjects that they will have daily contact for the next 7 days.

#### **5.2.5 Daily Telephone Contact for Seven days after an Experimental Session**

- a. Starting on the day of the integrative psychotherapy session following each experimental session, one of the therapists will contact the subject via telephone or in person on a daily basis for one week.
- b. The integrative contact will be for a brief check-in lasting 5 to 15 minutes, or as long as necessary to address any subject's concerns and to assess subject's well-being. Additional telephone contact can be initiated at the request of the therapists or subject.
- c. On the second and seventh day of contact after the experimental session, the subject will complete the C-SSRS.
- d. General wellbeing will be assessed at each phone call.
- e. Spontaneously reported reactions, AEs and Medications will be collected as described in Sections 8.5 and 9.0 of the protocol.

#### **5.2.6 Integrative Psychotherapy Between Experimental Sessions (Visits 6, 7, 10 and 11)**

- a. The subject will have two additional integrative psychotherapy sessions lasting at least an hour with at least one of the therapists from the subject's therapist team between each experimental session. The therapists may conduct more sessions if they and the subject deem it necessary.
- b. Record each integrative session to audio and video. Subjects may receive a copy of one or more integrative sessions upon request.

- c. The C-SSRS will be administered just prior to beginning each integrative session.
- d. General wellbeing will be assessed at each integrative session.
- e. The subject will complete the PDS questionnaire on the third integrative session.
- f. The subject and therapists will continue to work on supporting the subject as she or he considers his or her experiences during experimental sessions.
- g. The therapists 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 therapists may arrange to work on reducing the distress at a specially scheduled integrative therapy session, through continuing contact, or at the next regularly scheduled integrative therapy session. The subject may also initiate contact with the therapists at any time throughout the study.
- h. AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.
- i. 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.

### **5.2.7 Evaluation at End of Stage 1 and Unblinding (Visit 12)**

The final evaluation in Stage 1 will occur two months after the second experimental session. This visit will consist of two meetings that may be completed on separate days, one with the independent rater and the other with the therapists.

- a. Subjects will meet the independent rater for at least an hour and a half.
- b. The blinded independent rater will administer:
  - CAPS to assess PTSD symptoms
  - PDS to assess self-reported PTSD symptoms
  - BDI-II to assess depression symptoms
  - GAF to assess general psychological function
  - PSQI to assess sleep quality
- c. The blinded independent rater will provide their belief of the subject's condition.
- d. After completing all assessments and measures with the independent rater, the subject will meet with the therapists for approximately 30 minutes.
- e. The therapists will assess suicidality with the C-SSRS.
- f. General wellbeing will be assessed.
- g. The blind will be broken for the subject's condition assignment. The independent rater will remain blind to condition assignment at this time.
- h. If the subject has received active placebo dose MDMA in Stage 1, the therapists will discuss enrollment in Stage 2. (See section 5.2.8)
- i. 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.
- j. Subjects who are not enrolled in Stage 2 may return to taking psychiatric medications if necessary.
- k. Subjects not enrolled in 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.

1. AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.

### **5.2.8 Open Label Stage 2 for Active Placebo Subjects**

- a. Subjects will be reminded that participation in Stage 2 is voluntary and optional.
- b. 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 two experimental sessions.
- c. Assessment of PTSD symptoms at the end of Stage 1 will serve as baseline assessments in Stage 2.
- d. If the start of Stage 2 is delayed for more than 30 days from the time of the last CAPS in Stage 1 to the first preparatory session in Stage 2 (Visit 13), the independent rater will re-administer the CAPS, PDS, BDI-II, GAF and PSQI, and these scores will be used as the baseline for comparison to assessment at the end of Stage 2.
- e. Subjects entering Stage 2 will meet with both therapists for a single review and preparatory psychotherapy session (Visit 13).
- f. Subjects will receive two open-label MDMA-assisted therapy sessions (V14, 18).
- g. Subjects will have the same sequence of sessions and integrative therapy as in Stage 1. Visits will be scheduled consecutively according to the Time and Events Table 3.
- h. Subjects will complete the PDS on the third integrative session.
- i. The same safety measures will be administered during Stage 2, including C-SSRS before, during and after each open-label session, vital signs and SUD during each open-label session.
- j. Spontaneously reported reactions, AEs and Medications will be collected and reported as described in Section 8.5 and 9.0 of the protocol.

### **5.2.9 Evaluation at the End of Stage 2**

Treatment effects will be assessed at the end of Stage 2. This visit will consist of two meetings that may be completed on separate days, one with the independent rater and the other with the therapists.

- a. Subjects will meet the independent rater for at least an hour and a half.
- b. The blinded independent rater will administer:
  - CAPS to assess PTSD symptoms
  - PDS to assess self-reported PTSD symptoms
  - BDI-II to assess depression symptoms
  - GAF to assess general psychological function
  - PSQI to assess sleep quality

- c. After completing all assessments and measures with the independent rater, the subject will meet with the therapists for approximately 30 minutes.
- d. The therapists will assess suicidality with the C-SSRS.
- e. General wellbeing will be assessed.
- f. The subject will complete the Responses to Research Participation Questionnaire (RRPQ).
- g. Subjects may return to taking psychiatric medications if necessary.
- h. 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.
- i. AEs and medications will be collected as described in Sections 8.5 and 9.0 of the protocol.

### **5.2.10 Long-Term Follow-up**

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 therapists.

- a. The independent rater will administer the CAPS, PDS, BDI-II, GAF and the PSQI.
- b. Subjects will have a final meeting with at least one of the therapists to review specified AEs and medications since the last visit. Subjects should bring the Memory Aid Cards to this visit, to be used as aids in recollection. These cards will not be collected. AEs and Medications will be collected as described in Sections 8.5 and 9.0 of the protocol.
- c. The therapists will assess suicidality with the C-SSRS.
- d. General wellbeing will be assessed.
- e. Subjects will complete a questionnaire assessing positive and negative long-term effects of the study.
- f. Subjects will complete the termination visit at this time.

### **5.3 Randomization and Subject Numbering**

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "001". Subjects who meet all inclusion and no exclusion criteria will be enrolled into the study and will be assigned a five-digit subject number. The first two digits will be "09" and will identify the protocol number. 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 09001, second 09002, etc.

In total, ten subjects will be enrolled into the study. The first two subjects will be enrolled in the open-label lead-in and assigned to the full dose condition. The subsequent

eight subjects will be enrolled in the randomized Stage 1. The randomized portion of the study will be blinded and there will be a 5/3 ratio between subjects in the Full Dose and Active Placebo conditions. An unblinded randomization monitor will generate the randomization list. Subjects will be assigned subject numbers consecutively, and subjects will be randomized in a blinded fashion. Upon enrolling a subject, the investigator will be provided with an Enrollment Code for that subject. Randomization numbers will be pre-printed on the container labels corresponding to doses for individual sessions. Randomization will be performed at least 24 hours before the experimental session for each subject. The therapists will utilize a web-based randomization program to obtain the container assignment for each experimental session. Blinded personnel will conduct all study evaluations in the randomized portion of the study until the blind is broken for each subject at the end of Stage 1. Detailed instructions will be provided to the site in a separate document.

#### **5.4 Removal or Withdrawal of Subjects from the Study**

Subjects can withdraw consent at any time without prejudice. The therapists 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 therapists withdraw a subject from the session, the therapists 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 by at least one of the therapists, 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 evaluation visits will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the therapist and/or Sponsor.

Individuals who replace subjects who withdraw from the open label lead-in and Stage 1 will be assigned the next available subject number. Lead-in subjects will be replaced if they withdraw between the first and second experimental sessions. Lead-in subjects who withdraw after the second experimental session will not be replaced. If Stage 1 subjects withdraw from the study before 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 investigator will be provided with sealed emergency unblinding envelopes corresponding to each Enrollment Code. These sealed envelopes will be stored in a secure limited access area and should remain sealed if there are no emergency unblinding events during the study. The therapists, independent rater, and subject will remain blind to condition assignment until unblinding at the end of Stage 1, at which point the subject and therapists, but not the independent rater, will learn an individual's condition assignment. Unblinding at the end of Stage 1 will be done using the web-based



randomization program. Detailed instructions will be provided to the site in a separate document.

## **5.5 Premature Discontinuation of the Study**

The Sponsor or the principal 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 retention and storage of 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.

## **6.0 Investigational Product**

### **6.1 Description of Active Compounds**

The experimental active 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 (Battaglia 1988, Setola 2003, Verrico 2007). Its direct actions on serotonergic, adrenergic and other receptors are considerably lower.

### **6.2 Preparation and Administration**

The study will consist of an open-label lead-in, where two subjects will receive a full dose of 125 mg possibly followed by a dose of 62.5 mg. The remaining eight subjects will enroll in the double-blind Stage 1 where subjects will be randomized to the two conditions described in Table 5 below. The blind will be broken for each subject when they reach the end of Stage 1. The subjects who received the active placebo dose of MDMA during the randomized study will be offered the opportunity to enroll in an open-label Stage 2 where they will receive full dose MDMA-assisted psychotherapy. Stage 2 visits will be conducted in a manner similar to Stage 1.

#### **6.2.1 Doses**

**Table 5. Doses of MDMA**

Number of Subjects	Condition	Blind?	Initial Dose	Supplemental Dose	Cumulative Dose
<b>2</b>	<b>Lead-jn</b>	Open Label	125 mg	62.5 mg	187.5 mg
<b>3</b>	<b>Active Placebo Dose</b>	Blinded	25 mg	12.5 mg	37.5 mg
<b>5</b>	<b>Full Dose</b>	Blinded	125 mg	62.5 mg	187.5 mg
<b>3 or less</b>	<b>Stage 2</b>	Open Label	125 mg	62.5 mg	187.5 mg

### 6.2.2 Compounding

MDMA in bulk has been provided by Lipomed AG, Switzerland to the Beer Yaakov Pharmacy and compounded by the appropriate pharmacist with the inactive compounds. MDMA is weighed into capsules of 125, 62.5, 25 and 12.5 mg (calculated as the weight of the hydrochloride salt), with capsules for initial dose different in color from capsules for supplemental dose. Additional inactive material (lactose) is used to ensure that active dose capsules are of equal weight to full-dose capsules. Capsules for the initial dose are a different color from capsules used for the supplemental dose, or should be otherwise clearly labeled as such.

### 6.2.3 Labeling

The primary and supplemental doses of MDMA for a single subject to complete one experimental session will be stored in a single box labeled with the protocol number, drug name, lot number, unique box number, Sponsor name and a statement that the drug is for clinical trial use only (see box label). Each dose of MDMA for each experimental session will be labeled and stored individually within the box (see container labels for each session and dose). Labels will be provided by the Sponsor and applied by the pharmacist. The box and container labels will be hidden from the investigator and therapists to assure blinding. All drug labels will comply with local regulations.

Box Label
MAPS Study# <u>XXXX</u>
Investigational Product: MDMA
Dose: Blinded (25 mg, 12.5 mg OR 125 mg, 62.5 mg)
Randomization # <u>XXX</u>
Subject Number _____
Lot #: XXXXX
Administer as per protocol
Caution-Limited by Law to Investigational Use Only

Container label
MAPS Study # <u>XXX</u>
Container # <u>XXX</u>
Subject # _____
Stage 1 MDMA
Administer as per protocol
Investigational Use Only

Container label
MAPS Study # <u>XXX</u>
Subject # _____
Stage 2
125mg & 62.5mg MDMA
Administer as per protocol
Investigational Use Only

Each dose will consist of the specified amount of racemic MDMA mixed with an inactive substance, such as lactose, to prevent the therapists from distinguishing doses through weight or appearance of the capsules. Initial doses will be distinguished from supplemental doses through labeling them to ensure that the correct dose is administered at the scheduled time. Each dose of MDMA will be administered along with a glass of water or electrolyte-containing fluid. MDMA will be administered in the same manner during each of the two experimental sessions in Stage 1. Doses for use in Stage 2 will all consist of capsules containing 125 mg MDMA for the initial and 62.5 mg MDMA for the supplementary dose.

### **6.3 Drug Accountability**

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

### **6.4 Drug Storage and Handling**

MDMA is a Schedule 1 compound and will be stored and handled in compliance with all relevant local and international regulations. In accordance with these requirements, the license-holder or licensed pharmacist will be responsible for storing and dispensing the MDMA. It will be stored in a secure safe within the hospital pharmacy used to store methadone and other strictly regulated compounds, in accordance with or approved by national drug authorities.

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. All doses administered will be recorded on the appropriate accountability logs.

Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant national regulations.

### **6.5 MDMA Stability**

The MDMA 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% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. 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. The most recent quality control analysis was performed by Prof. Dr. R. Brenneisen, DCR, University of Bern, Switzerland on February 2, 2010. This analysis

reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94. 1 B5.5 with no decomposition products detectable and an HPLC purity 99.9%.

## **7.0 Risks of Participation**

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

In preparation for drug-assisted psychotherapy 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 drug-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, 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. 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 researchers or regulatory agencies.

### **7.2 Risks of Receiving MDMA**

Spontaneously reported reactions and common adverse effects of MDMA are modest and have generally not been associated with serious discomfort by healthy volunteers in previous studies. Common reactions include lack of appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, ruminations, and thirst. Other slightly less common reactions include restlessness, paresthesias (odd somatic feelings, such as tingling, feeling hot or cold), impaired judgment, perspiration, drowsiness, and nystagmus (eye-wiggling). While anxiety, headache, fatigue, insomnia and lack of appetite were spontaneously reported by 40% to 80% of participants in both conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by participants in

the MDMA than the placebo condition, and irritability was slightly more likely to be reported in the placebo condition. Additionally, participants in the MDMA condition were more likely to report muscle tension in various body parts and diarrhea. 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, needing more sleep, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects are reported less often than acute effects. More information on spontaneously reported reactions is described in the Investigator's Brochure.

MDMA may produce mild alterations in sensory perception and altered perception of time [48, 67, 93]. Women may be more sensitive to these effects [68]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change while driving [54]. For this reason, subjects will stay at the site overnight and will not be permitted to drive after experimental sessions.

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.

Further information on the risks associated with MDMA, including information drawn from case reports and studies of ecstasy users, can be found in the Investigator's Brochure.

### **7.2.1 Cardiovascular and Sympathomimetic 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. These changes should last no more than six hours. In less than 5% of volunteers in Phase 1 studies, increases in blood pressure were higher than 140/90 mmHg. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of participants and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity. For more information, see the Investigator's Brochure.

Risks posed by elevated blood pressure will be addressed by excluding people with hypertension and monitoring blood pressure and pulse as described in Safety Measures section 5.1.2. During experimental sessions the co-therapists will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. Subjects reporting chest pain, shortness of breath or neurologic symptoms or other potential indicators of hypertension will have more frequent measurements. Any participant who experiences sustained blood pressure of > 220 systolic or > 120 diastolic or heart rate > 75% predicted maximum during the first experimental session will not be given a second experimental session.

In case of need, subjects will be transferred to the emergency room at Assaf Harofeh Hospital. Subjects who are transferred will be accompanied by a physician or paramedic from the ICU of Magen David Adom. Reasons for moving a patient to an ICU would include, but not be limited to, severe headache in the setting of hypertension, angina or neurological deficits regardless of blood pressure. In the case of an emergency, intravenous anti-hypertensive agents will be available in addition to the usual resuscitation drugs and equipment. The investigator and co-therapists may, at any time, make a clinical judgment to transfer the patient to the ICU for closer monitoring and additional treatment.

The co-therapists will be prepared to respond to rare complications of cardiovascular effects, such as stroke or myocardial infarction. The co-therapists will attend to any signs or symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress. If any participant has neurological deficits, whether or not they are associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as described above. He or she will be transported to the emergency department at Beer Yaakov Hospital for further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the 3 hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [94, 95].

The co-therapists will observe the participant and note any complaints of chest pain. If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will undergo a stat ECG, receive oxygen and an IV and will be monitored as described above. If necessary, he or she will be transported to ICU or a location in the hospital where appropriate care can be given. He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the participant has had an acute myocardial infarction (AMI), he or she will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [96].

### **7.2.2 Psychological Distress**

Mild anxiety and depressed mood are occasionally reported 1–3 days after MDMA administration [45, 68, 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 therapists, with occasional use of benzodiazepines for anxiety. In this 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 reactions. 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 therapists upon request or at the appearance of signs of a potential serious 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 experimental session, including empathic listening on the part of the therapists 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 experimental session, the therapists will remain with the subject for at least two more hours. During this time, the therapists 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 preparatory session. If this situation should occur during an integrative therapy session, at least one of the therapists 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 clinical investigator will decide between the following options:

1. A psychiatric nurse, therapeutic assistant or therapist will stay with the subject until the time of his or her appointment with therapists the next day. The therapists will then meet with the subject daily until the period of destabilization has passed.
2. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an MDMA session, the therapists may prescribe a benzodiazepine or zolpidem as a “rescue medication.” This medication will be captured on the concomitant medications CRF page. Therapists 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 therapists.
3. Hospitalization for stabilization. If a subject should become psychotic arrangements will be made to stabilize them and transfer them to the 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 [68], and ambient temperature does not enhance or attenuate this slight elevation in humans.

If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, ice packs will be used, blood will be drawn for stat CBC, electrolytes, BUN/creatinine, glucose, CPK, PT, PTT, platelets and liver enzymes, and urine will be collected for urinalysis.

### **7.2.4 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 [97, 98], as discussed in the Investigator’s Brochure.



Pregnant and lactating women will be excluded from participation in the study, 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.

#### **7.2.5 Potential Neurotoxicity Associated with Ecstasy Use**

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [99]. However, they are basing their case on studies that employed inappropriately high doses of MDMA utilized in animal studies, and on human studies comparing the effects of repeated use of ecstasy, often along with other drugs. We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. More information on the potential neurotoxicity of MDMA can be found in the Investigator's Brochure.

#### **7.2.6 Risk Mitigation**

Careful review of medical screening data will be utilized to exclude potential participants with preexisting exclusionary medical conditions from the study. Study procedures have been developed to mitigate the risks of receiving MDMA described in detail in the Investigator's Brochure. Ambient temperature will be kept at a comfortable level during experimental sessions. Subjects will not be allowed to drink more than 3L of fluids over the course of the experimental session, and fluid intake will be spread out appropriately during the session. Fluids administered will include electrolytes. If a participant exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after the first experimental session, then he or she will not receive a second experimental session.

### **7.3 Abuse Liability**

Findings in humans and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine. More information on abuse liability is provided in the Investigator’s Brochure

Whether or not MDMA's abuse potential will negatively affect people with PTSD exposed to MDMA when given along with psychotherapy is an open question for which there is of yet no direct data. Mithoefer and colleagues are in the process of analyzing data from a long-term follow-up of participants in their study of MDMA-assisted psychotherapy. Only one of 20 participants took Ecstasy after completing the study and failed to reproduce the experience with the therapists, and a number of participants volunteered that they would never seek out Ecstasy outside a legal, controlled therapeutic setting.

Diversion is not an issue in this protocol because MDMA will only be administered a few times under the supervision of the clinical investigator and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

## **8.0 Adverse Events**

### **8.1 Adverse Events**

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

An *unexpected adverse event* is one that is not listed in the current Investigator’s Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored by the therapists until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the investigator and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

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

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

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

1. Not Related

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

2. Possibly Related

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

3. Probably Related

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

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

## **8.2 Spontaneously Reported Reactions**

Commonly expected spontaneously reported reactions are collected on a separate CRF page and will be categorized as mild, moderate or severe. Common, expected reactions are defined as those most frequently reported in the literature and include: Anxiety, Diarrhea, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Heavy Legs, Impaired Gait/Balance, Impaired Judgment, Increased Irritability, Insomnia, Jaw Clenching or Tight Jaw, Lack of Appetite, Low Mood, Muscle Tension, Nausea, Need More Sleep, Nystagmus, Parasthesias, Perspiration, Restlessness, Rumination (increased private worries), Sensitivity to Cold, Thirst, and Weakness. Spontaneously reported reactions 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 a study-related SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

#### **8.4 Medical Emergencies**

The sessions will be conducted in a general medical setting where emergency equipment will be immediately available, medical staff and experienced nurses will be on hand and there will be ready access to specialty medical back up and intensive care beds if necessary. Participants will have a means of contacting the clinical investigator if any problem occurs. 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 therapists will be able to stabilize study subjects and then transport them to the emergency department or ICU at Beer Yaakov Hospital. In case of need, subjects will be transferred to the emergency room at Assaf Harofeh Hospital. Subjects who are transferred will be accompanied by a physician or paramedic from the ICU of Maguen David Adom.

## **8.5 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 Clinical Investigator (CI) or designee 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 spontaneously reported reactions will be collected on the day of drug 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 Memory aid card will be provided to the subject on the last visit prior to the 12 month follow up to record information on medications taken to treat SAEs, AEs leading to withdrawal and psychiatric AEs during the period between the end of Stage 1 or end of Stage 2 and the 12 month follow-up evaluation. The memory aid card will not be collected, but information from the card will be used to aid the subjects in providing information to the investigator. This information may be collected by phone.

## 9.0 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 tapering with his or her outside treating physician, if any, and will be required to give the therapists 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 session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life).

If a subject is using marijuana at least two months prior to administration of the baseline CAPS, the prospective subject will be encouraged to abstain from using marijuana during the study, and required to abstain during the period beginning 3 days prior to each experimental session as assessed by self-report. Subjects may resume marijuana use on the 8<sup>th</sup> day after each experimental session. The same period of cessation of use will be required from Stage 2 participants. Participants who choose to use marijuana during the study will be given a document, "Reminder of Study Rules for Subjects Using Marijuana," as a reminder for when they must refrain from using marijuana and what information about their marijuana use will be asked by the clinical study staff. Frequent marijuana users may test positive in a urine drug test up to one month after cessation. Subjects will be asked to report on their marijuana use (frequency, dose, route, and reason for use) at baseline and during the course of the study. Baseline measurements and experimental sessions will be conducted despite a positive urine drug test for marijuana.

The therapists will request information about any changes in medication just prior to each experimental session. All medications, over the counter (OTC), marijuana, 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 8.5 and all changes including discontinuations or additions to psychiatric medications will be collected. Medications 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). Rescue medications may be benzodiazepines, as lorazepam or zopiclone. 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 as described in Section 8.5. 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 clinical investigator or study staff will examine laboratory assessments gathered in screening for assessing participant eligibility. The investigator will use a list of normal ranges to conclude whether participants are eligible for the protocol, and will indicate justification for admitting participants with abnormal values.

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

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

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

**CBC**, which includes:

Hematocrit;  
hemoglobin;  
MCV;  
MCH;  
MCHC;  
RDW;  
percentage and absolute differential counts;

RBC;  
red cell count;  
WBC;

**Urinalysis**, which includes:

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

**Thyroid function**, which includes:

TSH high sensitivity;  
Free T4;  
Free T3.

In addition, HIV serology will be performed.

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

The identity of the laboratory that will perform assessments other than the urine drug screen and pregnancy test will be provided on a separate document.

The urinary pregnancy tests and drug tests will be performed at the study site.

## **11.0 Study Monitoring, Auditing and Documentation**

The Clinical Investigator, therapists and their study staff will be trained prior to the start of the study. 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 in order to comply with GCP guidelines and to ensure validity of the study data. During each monitoring visit, source data verification will be performed 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 will be supplied in a separate document. For detailed monitoring information, please see the study Monitoring Plan.



During or after the study, the regulatory authorities, the IRB, and/or representatives of the Sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

## **12.0 Data Analysis**

The Sponsor will examine CAPS, PDS, BDI-II, GAF and PSQI scores at baseline and two months after the second experimental session at the end of Stage 1 in Active Placebo and Full Dose conditions with independent sample t-tests for baseline scores. When MDMA and Active Placebo scores are not significantly different at baseline, a second independent sample t-test will examine the scores at the end of Stage 1, with p. set at 0.05. Subsequent independent sample t-tests will be applied to scores where there are significant differences in baseline values, with p. set at 0.05.

A repeated measures analysis of variance (ANOVA) will be performed upon PDS scores at baseline, after the third integrative session (Visit 7), the sixth integrative session (Visit 11) and at the end of stage 1, with p. set at 0.05. Condition (active placebo or full dose MDMA) will serve as a between-subjects factor. PDS and CAPS scores will be correlated at baseline and at the end of Stage 1 to examine the degree to which the two measures arrive at similar symptom severity scores.

Formal statistical comparisons between Stage 1 and Stage 2 scores may only occur if all three eligible participants enroll in Stage 2. Lead-in subjects will be compared statistically to Stage 2 subjects, and data from lead-in subjects will only be utilized if they are equivalent to Stage 2 subjects. The sponsor will perform an analysis comparing CAPS and BDI-II scores after experimental and open-label sessions for participants in the full dose condition and another analysis for participants enrolled in Stage 2. Descriptive statistics will be computed for PDS scores for the end of Stage 1, the third and sixth integrative sessions of Stage 2 (Visits 17 and 21) and the end of 21. The sponsor will examine CAPS, PDS, GAF, BDI-II and PSQI scores 12 months after the final MDMA-assisted psychotherapy session. If there is enough data available for formal comparisons, the Sponsor will use a repeated measures ANOVA with baseline, end of Stage 1 and end of Stage 2 scores as repeated measure at p. set at 0.05.

Descriptive statistics will be calculated for all measurements overall and within the two dose conditions. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. Effect size of Active Placebo and Full Dose MDMA for all outcome measures for Stage 1, Stage 2, and 12 months after the final experimental session will be estimated using Cohen's techniques.

There is no expectation that conditions will differ in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, as depression. However, owing to small sample size, such variations may arise by chance.

The therapists will record average baseline and post-drug peak blood pressure, heart rate and body temperature for participants during experimental sessions. The therapists will also record spontaneously reported reactions and AEs as described in section 8.5. Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The sponsor will informally or formally compare peak blood pressure, heart rate and body temperature for participants after sessions with Active Placebo or Full Dose MDMA. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

An interim analysis may be completed when all participants have completed the main study, including stage 1 and Stage 2, but not all participants have completed the 12-month follow-up evaluation. Additionally, an interim analysis may be performed after all participants have completed Stage 1 but not necessarily before all eligible participants complete Stage 2. This analysis will address both safety and efficacy of the treatment.

### **12.1 Statistical Power**

This is a pilot study, and as such, power analysis was not conducted for the study. The study is underpowered for detection of differences of a small or moderate effect size, and it may detect differences if the effect size is large.

Analyses of MAPS' completed US study of MDMA-assisted psychotherapy in 20 people with PTSD found an effect size of 1.24 for treatment efficacy, as represented by changes in CAPS score [2]. The estimated effect size for this study may be lower as a result of comparing the full dose of MDMA with a low dose of MDMA instead of with inactive placebo, small sample size and unequal distribution of conditions. The sponsor intends to pool data across studies or perform meta-analyses of CAPS scores across all pilot studies.

The sponsor used Java applications created by Lenth and posted on the website listed below to calculate estimated statistical power for this study, assuming an effect size of 0.8 for the impact of two sessions of MDMA-assisted psychotherapy on symptoms of PTSD and depression [100], reducing the effect size to account for the hypothesized effects of using an active placebo. The software calculated an estimated power of 0.15, indicating an underpowered study. Had we used the higher effect size of 1.1, power analysis still indicates that this study is underpowered, with an estimated effect size of 0.25. Without previous data concerning the effects of MDMA-assisted psychotherapy upon sleep quality, no power estimates have been made for differences in sleep quality between full dose and active placebo participants.

### **13.0 Ethics**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The protocol and the proposed informed consent form must be reviewed and approved by local regulatory agencies and a properly constituted ethics board before study start. Signed and dated documentation that the protocol and informed consent have been approved by the ethics board and local agency must be provided to the sponsor. Prior to study start, the Clinical Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor.

#### **14.0 Informed Consent**

The therapists are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), ethics board approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The informed consent should include access to original medical records and processing of coded personal information. 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 process of obtaining informed consent should be documented in the subject source documents.

The therapists 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 informed consent form, and written information should receive approval from an ethics board before use.

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

#### **15.0 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.

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. Full names and addresses will not appear in these recordings.

### **16.0 Costs to Participants**

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. The Sponsor will not cover medical expenses related to injuries which occur during the study period that are not directly related to study procedures.

### **17.0 Treatment and Compensation for 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 coverage protects the Sponsor, the institution and the investigators from any legal actions pursued against them.

### **18.0 Record Retention**

Investigators must retain all study records required by the Sponsor and applicable ICH-GCP and local regulations in a secure and safe facility. The investigator must consult a representative of the Sponsor 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.

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