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A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Subjects 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
DBP	Diastolic Blood Pressure
DEA	Drug Enforcement Administration
DES-II	Dissociative Experiences Scale II
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
ECG/EKG	Electrocardiogram
ED	Emergency Department
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
F	Fahrenheit
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
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
IR	IR
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

MP-2	MAPS' second clinical trial of MDMA-assisted psychotherapy for PTSD
PDS	Posttraumatic Diagnostic Scale
PRN	As needed
PSQI	Pittsburgh Sleep Quality Index
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-I-RV	Structured Clinical Interview for Diagnoses Axis I Research Version
SERT	Serotonin Transporter
SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SOCQ	States of Consciousness Questionnaire
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
S-WAI-O	Segmented Working Alliance Inventory – Observer Form
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

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval as a clinical trial sponsor for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with chronic posttraumatic stress disorder (PTSD). This study is a part of a global series of Phase 2 pilot clinical trials designed to evaluate the safety and efficacy of MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD, as preparation for Phase 3 studies and possible use as an approved prescription medication.

MAPS has published results showing clinically and statistically significant improvements in PTSD severity from 20 subjects treated in their first pilot study (MP-1) in the United States (U.S.) [1]. Findings from the long-term follow-up of MP-1 subjects suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [2]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) in 12 subjects suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [3]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. Ongoing and planned Phase 2 studies, along with the study described in this protocol, are laying the groundwork for an eventual End-of-Phase 2 meeting with FDA and possible Phase 3 multi-site MDMA/PTSD research studies.

This Phase 2 pilot study will examine the safety and efficacy of manualized MDMA-assisted psychotherapy in 12 subjects with chronic, treatment-resistant PTSD of at least 6 months duration who were unable to achieve remission despite having received prior treatment with either pharmacotherapy or psychotherapy of adequate dose/duration or who discontinued treatment due to lack of tolerability. Two types of co-therapist teams will conduct the study. The use of intern co-therapists working with experienced co-therapists will be compared to teams consisting of two experienced co-therapists. This study is also intended to continue the development of a manualized psychotherapeutic approach to this potential treatment.

2.2 Background

2.2.1 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. A complex biopsychosocial condition, PTSD is characterized by a combination of three types of symptoms: hyperarousal symptoms such as hypervigilance, anxiety and sleep disturbance, intrusive re-experiencing of traumatic experiences, such as intrusive memories, nightmares or flashbacks, and avoidance symptoms, including emotional numbing and withdrawal [4, 5]. The DSM-IV 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.

The lifetime prevalence of PTSD in the U.S. general population is between 6% and 10% [6-10], but it is common in other countries as well [7, 11-14]. According to some estimates, PTSD appears to be less prevalent in the general population of Europe at 1.9% [15]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [16], and it is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [17]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [18-20].

PTSD is clearly a serious public health problem and contributes substantially to healthcare costs [5, 8, 9]. PTSD is typically a chronic illness [6, 21] associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [7-10, 22]. People suffering from PTSD face challenges in relationships and work productivity [23]. Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [24]. Two selective serotonin reuptake inhibitors (SSRI), sertraline and paroxetine, which are known to affect the serotonergic components of PTSD, are currently marketed as PTSD medications in the U.S. [25, 26]. In addition, SSRIs must be used every day in order to be effective for PTSD symptoms [27], and are associated with a high rate of discontinuation due to lack of tolerability caused by treatment-emergent side effects that may be under-reported [28, 29].

A wider array of effective treatments are needed for PTSD. At least a third of PTSD patients fail to respond to established PTSD psychotherapies or do not respond in a clinically significant manner [30-32]. 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 [33]. Forty to 60% 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 still satisfied diagnostic criteria for PTSD based on high Clinician Administered PTSD Scale (CAPS) scores, and this was considered highly efficacious [34]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [25], and another randomized, double-blind study found no difference between sertraline and placebo in the treatment of PTSD [35]. These findings suggest that there is still a substantial need for innovative treatments for PTSD.

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 type of 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]. 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 [36] for a review). Examples of this are virtual reality-assisted exposure therapy [37, 38] and D-cycloserine-assisted psychotherapy [39]. MDMA-assisted psychotherapy is another such approach.

2.2.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 [40, 41]. MDMA is a monoamine releaser that has its greatest effects on serotonin, followed by norepinephrine and dopamine [42-47]. MDMA is capable of inducing unique psychopharmacological effects, including:

- Decreased feelings of fear.
- Increased feelings of wellbeing.
- Increased sociability and extroversion.
- Increased interpersonal trust.
- Alert state of consciousness.

Early observers noted increased acceptance of self and others, increased tolerance of emotionally upsetting materials and the ability to address these issues without extreme disorientation or ego loss [48-51]. In the U.S., MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists in the treatment of neuroses, relationship problems, and PTSD [48, 49, 52, 53] before it was placed in Schedule I in 1985 as a result of extensive non-medical use [51, 54, 55]. Placement in Schedule I prohibited it for use except in a federally approved research setting.

In contrast to daily administrations of SSRIs, MDMA-assisted psychotherapy consists of several drug-assisted sessions interspersed with a moderate course of non-drug psychotherapy. Thus the effects of MDMA are distinct from and go well beyond those of anti-anxiety drugs such as benzodiazepines. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users found a small percentage of people exhibit problematic use of ecstasy, (material represented as containing MDMA) [56, 57]. Studies of regular or problematic ecstasy users indicate that on average, regular use occurs no more often than once a week

[58]. Hence, MDMA may have moderate abuse potential. See the Investigator's Brochure (IB) for a more detailed explanation.

2.2.3 Previous Clinical Experience with MDMA

Classification as a Schedule I drug hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and effectiveness of MDMA-assisted psychotherapy has become more feasible due to an open IND with the FDA [59-61]. 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 [62]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting [62]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [62-68]. The noted elevation in body temperature was not clinically significant [1].

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 [69, 70]. 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 (AEs) or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 to 75 mg [70].

MAPS went on to sponsor the first U.S. Phase 2 study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD, designated as MP-1. This study employed the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded Independent Rater (IR) at baseline, three to five days after each experimental session, and two months after the final experimental session. Data from this randomized, placebo-controlled pilot study suggests that MDMA is associated with significantly greater improvement in PTSD than placebo (N=20) [71]. Findings from the long-term follow-up evaluating these subjects at an average of 41 months post-treatment suggests that the therapeutic benefits have been sustained over time on average, although two subjects experienced a relapse in PTSD symptoms [2]. The sponsor also supported a randomized, double-blind pilot study in 12 subjects with chronic, treatment-resistant PTSD in Switzerland with three experimental sessions. The study results suggested a trend toward significant improvement in subjects receiving full dose MDMA, when compared to 25 mg active placebo MDMA at two-month follow-up. The improvement continued to increase during the 12-month follow-up [3]. In addition, the sponsor supported an initial pilot study with two experimental sessions comparing full dose to 25 mg active placebo MDMA in Israel that enrolled five subjects, with no drug-related Serious Adverse Events (SAEs). Subjects reported benefits that were not reflected in CAPS scores, leading to termination of the study for additional training of the Israeli therapists and research team. Most recently, in the U.S., MAPS has commenced a follow-up to its initial U.S. trial with a PTSD relapse study, along with a second Phase 2 trial, specifically treating U.S. military veterans.

As of March 2013, MDMA has been administered to more than 790 research subjects, in both Phase 1 and Phase 2 studies, without any occurrences of unexpected drug-related SAEs [67, 72-85].

2.2.4 MDMA-assisted Psychotherapy for PTSD

In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [54]. 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].

Treatment goals of MDMA-assisted psychotherapy for PTSD include alleviating symptoms, interrupting and counteracting the stress-induced neurobiological abnormalities that may be associated with the condition. In fact, the biologic and psychotherapeutic approaches overlap and reinforce each other. Knowledge about the connections between the neurobiological and therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala [86], and attenuates amygdalar response to angry faces [87]. 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 [88-90]. The reduction in stress-induced activation of the amygdala may be supported and enhanced by interacting with the therapists during and after the MDMA experience.

Oxytocin is a neurohormone associated with pair bonding and social affiliation in mammals [91]. Oxytocin administration is associated with increased interpersonal trust and attenuated reactivity to threatening faces [92, 93], and some researchers have suggested a role for oxytocin in treating PTSD [94]. MDMA has been shown to elevate serum oxytocin in humans [66, 95]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [87]. The effects of MDMA on oxytocin may increase empathy or compassion for self and others, decrease defensiveness and strengthen therapeutic alliance. These factors taken together can provide the opportunity for a corrective emotional experience [48].

A combined treatment of MDMA and psychotherapy may be especially useful for treating PTSD because MDMA can attenuate the fear response of a perceived threat to one's emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [1, 49, 51, 70]. Elimination of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to information about them [48]. Subjects are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. MDMA seems to engender internal

awareness that even painful feelings that arise are an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of the trauma as a past event, a more accurate perspective about its significance and a heightened awareness of the support and safety that exists in the present. As a result MDMA-assisted psychotherapy may enable the subjects to restructure their intrapsychic realities and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

A comprehensive review of MDMA research is included in the IB supplied by the Sponsor. This document should be reviewed prior to initiating the protocol.

2.3 Protocol Purpose

This Phase 2 pilot study is a randomized, double-blind, dose response study in 12 subjects comparing the effects of low and full dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition of 125 mg of MDMA and five subjects will be randomized to the comparator dose condition of [redacted] Stage 1 of the study will consist of two blinded experimental sessions and one open-label experimental session of manualized MDMA-assisted psychotherapy, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. The study will be unblinded one month after the second experimental session in Stage 1 after completion of outcome measures, which constitutes the primary endpoint assessment. After unblinding, comparator dose subjects will have the opportunity to cross over to open-label Stage 2 and only full dose subjects will complete the third open-label experimental session. A blinded IR will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at equivalent points in Stage 2. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2. This study will provide an estimate of effect size based on dose response of PTSD symptoms to MDMA-assisted psychotherapy.

Two types of therapy teams will conduct psychotherapy visits according to the treatment manual provided. Four subjects will be treated by two teams consisting of two experienced co-therapists and eight subjects will be treated by an intern therapist paired with an experienced co-therapist. Information will be collected regarding consistency and response between the teams by reviewing adherence criteria and therapeutic alliance in blinded videos of therapy sessions. This study will also continue the refinement of the treatment manual.

2.4 Rationale of Dose Selection

This study will compare the effects of psychotherapy sessions assisted by full dose MDMA or comparator dose MDMA. The full dose will be 125 mg MDMA followed 1.5 to 2.5 hours later by 62.5 mg MDMA. The comparator dose will be [redacted] MDMA followed 1.5 to 2.5 hours later by [redacted] MDMA.

Table 1. Dose Regimen

	Initial Dose	Supplemental Dose	Cumulative Dose
Full Dose	125 mg MDMA	62.5 mg MDMA	187.5 mg MDMA
Comparator Dose	[redacted] MDMA	[redacted] MDMA	[redacted] MDMA

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 [62, 63, 65, 67, 79, 96-100]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [49, 51, 54]. 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 comparator dose of MDMA was chosen on the basis of its demonstrated ability to produce detectable subjective effects as a part of the sponsor's ongoing initiative to optimize the double blind in MDMA-assisted psychotherapy using dose response. It is very similar to doses used in Phase 1 studies [63, 68]. This dose is expected to produce increases in positive mood and tension, in combination with a lower degree of therapeutic effects than the full dose.

3.0 Protocol Objectives

The overall objective of this study is to examine whether the full dose of MDMA versus the comparator dose of MDMA used in conjunction with manualized psychotherapy will reduce or attenuate PTSD symptoms as evaluated by standard clinical measures and to collect safety data.

3.1 Primary Objective

- Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

3.2 Secondary Objectives

The following objectives will compare full dose subjects to comparator dose subjects in Stage 1:

- Assess changes in self-reported PTSD symptoms in subjects receiving the full dose MDMA and comparator dose MDMA as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory-II (BDI-II) at baseline and the primary endpoint.
- Assess quality of life with the Global Assessment of Functionality (GAF) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociation Experiences Scale II (DES-II) at baseline and the primary endpoint.

The following objectives will compare effects in specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, quality of life via GAF, sleep quality via PSQI, and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, and global function, sleep quality, dissociation symptoms via CAPS and PDS, BDI-II, GAF, PSQI, and DES-II one year after the final experimental session for each subject.

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

- Explore the effects of each experimental session upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Assess the effect of the third experimental session for full dose subjects in Stage 1 and Stage 2 using CAPS, PDS, BDI-II, GAF, PSQI, and DES-II.
- Assess the ability of the investigators and subjects to accurately guess condition assignment in Stage 1.
- Correlate adherence to the treatment manual with Global CAPS scores using adherence criteria ratings to assess videos of psychotherapy sessions.
- Correlate development of therapeutic alliance with Global CAPS scores using the Segmented Working Alliance Inventory-Observer Form (S-WAI-O) to assess videos of psychotherapy sessions.

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) and vital signs including blood pressure, heart rate, and temperature will be measured during each experimental session, and vital signs will be compared between subjects in each condition.
- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.
- Serious adverse events, adverse events, and spontaneously reported reactions will be collected during the study, as described in Section 8.5.

4.0 Protocol Design

This randomized, double-blind, dose response pilot study that will examine the safety and efficacy of MDMA-assisted psychotherapy in subjects diagnosed with chronic, treatment-resistant PTSD of at least six months duration. Stage 1 will include two blinded and one open-label MDMA-assisted psychotherapy session scheduled approximately one month apart with a male/female co-therapist team. There will also be a moderate course of preparatory and integrative psychotherapy sessions as described in the Time and Events Table.

There will be two types of male/female co-therapy teams treating subjects, one type will have two experienced psychotherapists and the other type will have one of the experienced psychotherapist placed with an intern therapist. The two experienced teams will treat four subjects total. Eight subjects will be divided between the two teams of experienced therapists working with interns. Each subject will be treated by the same co-therapist team in psychotherapy sessions throughout the study in order to develop and maintain therapeutic alliance.

Upon enrollment, subjects will be randomly assigned to receive either full dose MDMA (seven subjects) or comparator dose MDMA (five subjects). In Stage 1, subjects will meet with their therapist team for three preparatory sessions and two blinded experimental psychotherapy sessions of MDMA-assisted psychotherapy. After each experimental session, subjects will stay overnight at the site and complete an integrative psychotherapy session the next day, followed by daily telephone calls for the next seven days and two additional integrative sessions. One month after the second experimental session, the primary endpoint assessment will take place, after which the blind will be broken. Subjects who receive the full dose will receive a third open-label experimental

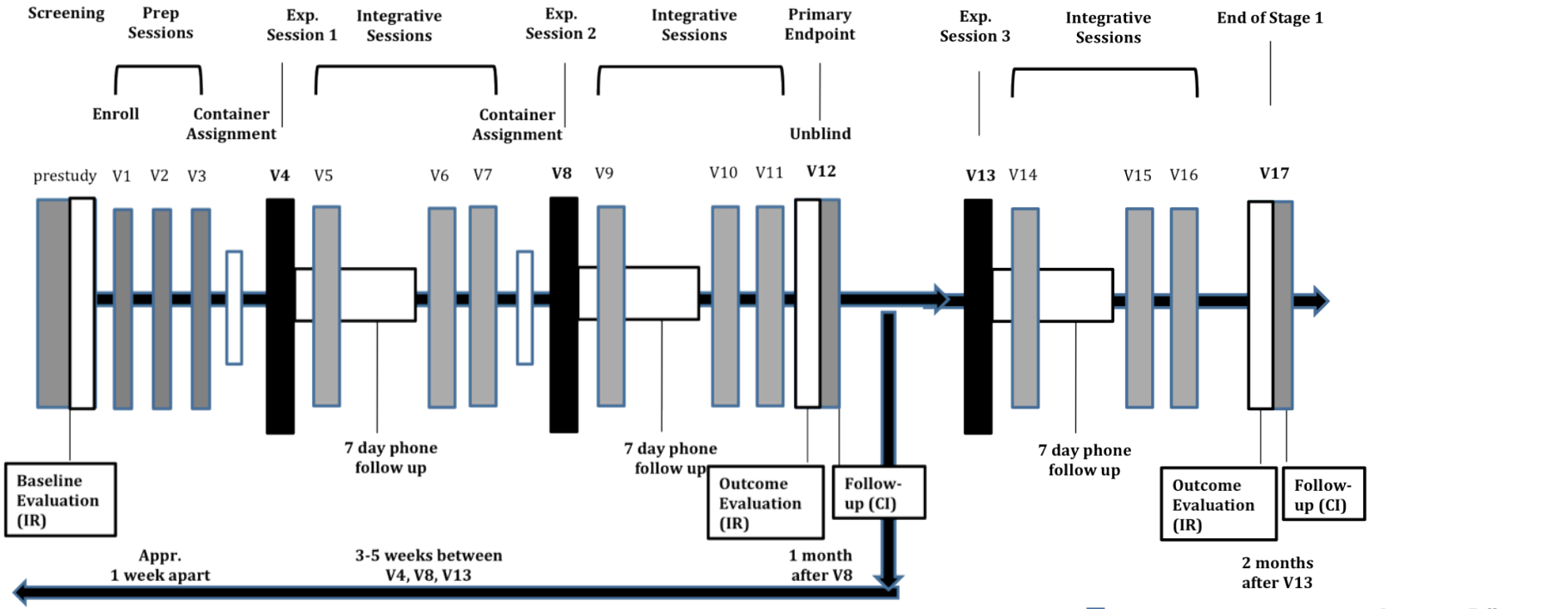
session with similar procedures. Subjects who receive the comparator dose will be offered the option to continue to the open-label Stage 2 unless they meet any exclusion criteria for study participation. In Stage 2, subjects will receive full dose MDMA in three experimental sessions that will otherwise follow the same sequence of events after a single preparatory session. (See Time and Events Table).

A blinded IR will administer outcome measures. The IR will assess PTSD symptoms with the CAPS, quality of life with the GAF, symptoms of depression with the BDI-II, sleep quality with the PSQI, and dissociation with the DES-II. The subjects will complete the PDS, a self-report measure of their PTSD symptoms, to provide correlations with measures administered by the IR.

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 complete a follow-up occurring two months after their last experimental session in Stage 1 and Stage 2, if applicable. 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 (see Time and Events Table).

The Sponsor will conduct an ongoing review of videotapes of psychotherapy sessions, entry criteria, vital signs, and reaction data for completed sessions and any AEs. The sponsor will provide ongoing feedback to the co-therapist teams to ensure proper therapist training, subject safety, and to ensure standardization of therapy techniques in the Sponsor's ongoing effort to manualize MDMA-assisted psychotherapy.

Stage 1 Summary of Events



Stage 2 Summary of Events

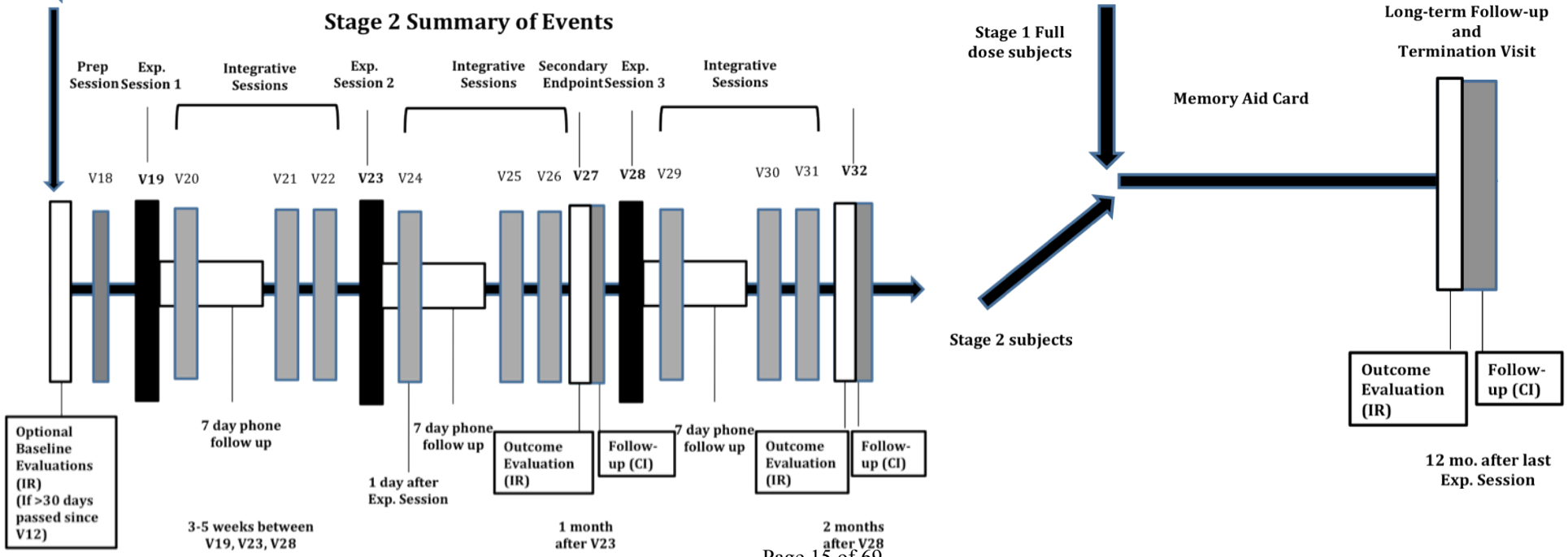


Table 2. Time & Events Stage 1

Study Phase	**Screen/ Baseline**	**Preparatory Sessions**	**Experimental Session 1**		**Experimental Session 2**		**Primary Endpoint**	**Experimental Session 3**		**End of Stage 1**
Visit #	Prior to enrollment	V1,2,3	V4	V5,6,7	V8	V9,10,11	V12	V13 [N]	V14,15,16 [N]	V17[N]
Type of Visit	Screening/ Baseline	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Experimental	Integrative	Outcome
Visit Timing	Over up to 2 months prior to V1	+/- 1 week apart	3-5 weeks post baseline	Between V4 and V8	3-5 weeks post V4	Between V8 and V12	1 month post V8	After V12	Between V13 and V17	2 months post V13
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Physical Exam, ECG	✓									
Brief Neurological Exam	✓									
SCID (IR)	✓									
Clinical Lab Tests, w/ HIV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication Taper (if applicable)		✓								
Study Enrollment if eligible		✓[O]								
Record to Audio/Video		✓	✓	✓	✓	✓		✓	✓	
General Well-Being		✓	✓	✓	✓	✓	✓	✓	✓	✓
Drug Screen	✓		✓		✓			✓		
Pregnancy Screen (if applicable)	✓		✓		✓			✓		
Obtain container assignment			✓[B]		✓[B]					
CAPS, GAF, BDI-II, PSQI, DES-II	✓						✓[L]			✓
PDS	✓			✓[M]			✓		✓[M]	✓
C-SSRS	✓	✓[G]	✓[C,D,E]	✓[I]	✓[C,D,E]	✓[I]	✓	✓[C,D,E]	✓[I]	✓
Administer Drug + Therapy			✓		✓			✓		
Monitoring of BP, Pulse, and Temp.			✓		✓			✓		
SUD			✓[E,F]		✓[E,F]			✓[E,F]		
Belief of Condition Assignment				✓[K]		✓[K]			✓	
Overnight Stay, SOCQ			✓		✓			✓		
Integrative Therapy Session				✓[A]		✓[A]			✓[A]	
7 days Telephone Contact				✓		✓			✓	
AEs Requiring Medical Attention			✓	✓	✓	✓	✓	✓	✓	✓
Spont. Reported Reactions & all AEs			✓[J]	✓	✓[J]	✓	✓	✓[J]	✓	
Changes in Tinnitus and/or Pain	✓[P]		✓[E,P]	✓[E,P]	✓[E,P]	✓[E,P]	✓[P]	✓[E,P]	✓[E,P]	✓[P]
AEs of psychiatric status or withdrawal		✓	✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Issue Memory Aid Card										✓[H]
Unblinding							✓			
Perception of Third Session	✓						✓[N]			✓[N]
RRPQ										✓[H]

A = First Integrative session is one day after experimental session; B = At least 24 hours prior to experimental session; C = Approximately six hours post MDMA; D = At the beginning of the session; E = As needed;

F = Approximately every 60 minutes; G = Given on 2nd preparatory session after washout; H = Only for subjects starting long-term follow-up; I = Day 2 and Day 7 phone calls only; J = Reactions collected for seven days post experimental session; K = On the day of the first integrative session following the experimental session; L = One month after the second experimental session but before the third experimental session; M = On the day of the third integrative session; N = Full dose subjects only; O = Only on Visit 1; P = Only in subjects with pre-existing tinnitus and/or chronic pain.

Table 3. Time & Events Stage 2

Study Phase	**Preparatory Session**	**Experimental Session 1**		**Experimental Session 2**		**Secondary Endpoint**	**Experimental Session 3**		**End of Stage 2**		**Long-term Follow-up**
Visit #	V18*	V19	V20,21,22	V23	V24,25,26	V27	V28	V29, 30, 31	V32		LTFU
Type of Visit	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Experimental	Integrative	Outcome		Follow-up
Visit Timing	Within 1 month post V12*	1 week post V18	Between V19 and V23	3-5 weeks post V19	Between V23 and V27	1 month post V23	1 month post V23	Between V28 and V32	2 months post V28		1 year post V13 or V28
Confirm Informed Consent	✓										
Confirm Inclusion/Exclusion	✓										
Enrollment in Stage 2	✓										
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Record to Audio/Video	✓	✓	✓	✓	✓		✓	✓			
General Well-Being	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Drug Screen		✓		✓			✓				
Pregnancy Screen (if applicable)		✓		✓			✓				
CAPS, GAF, BDI-II, PSQI, DES-II	Use V13*					✓[H]			✓		✓
PDS	Use V13*		✓[I]			✓		✓[I]	✓		✓
C-SSRS	✓	✓[B,C,D]	✓[G]	✓[B,C,D]	✓[G]	✓	✓[B,C,D]	✓[G]	✓		✓
Administer Drug + Therapy		✓		✓			✓				
Monitoring of BP, Pulse, and Temp.		✓		✓			✓				
SUD		✓[D,E]		✓[D,E]			✓[D,E]				
Overnight Stay, SOCQ		✓		✓			✓				
Integrative Therapy Session			✓[A]		✓[A]			✓[A]			
7 days Telephone Contact			✓		✓			✓			
AEs Requiring Medical Attention	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Spont. Reported Reactions and all AEs		✓	✓[F]	✓	✓[F]		✓	✓[F]			
Changes in Tinnitus and/or Pain		✓[J,D]	✓[J,D]	✓[J,D]	✓[J,D]	✓[J]	✓[J,D]	✓[J,D]	✓[J]		✓[J]
AEs of psychiatric status or withdrawal	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Serious Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Perception of Third Session						✓			✓		
Complete Stage 2 go to follow-up									✓		
RRPQ									✓		
Issue Memory Aid Card									✓		
Follow-up Questionnaire											✓
Termination Visit											✓

* If Visit 18 is more than one month after Visit 12, then subjects will need to repeat measures prior to starting Stage 2.

A = First session is one day after experimental session; B = Approximately six hours post MDMA; C = At the beginning of the session; D = As needed; E = Approximately every 60 minutes; F = Reactions collected for seven days post experimental session; G = Day 2 and Day 7 phone calls only; H = One month after the second experimental session but before the third experimental session; I = On the day of the third integrative session; J = Only in subjects with pre-existing tinnitus and/or chronic pain.

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 the follow-up portion of the study, which encompasses 12 months after the final experimental session.

- Full dose subjects completing Stage 1 only: 15 months.
- Comparator dose subjects who continue and complete Stage 2: 18 months.

Screening may take up to two months. The time period between the end of Stage 1 and the start of Stage 2 should not exceed five months for any subject. Any delay between visits would result in a corresponding extension of study duration.

4.2 Recruitment and Subject Population

Subjects may be men or women aged 18 or older with a confirmed diagnosis of chronic, treatment-resistant PTSD who have undergone psychotherapeutic or psychopharmacological treatment for PTSD of adequate dose/duration without achieving remission. Subjects who discontinued PTSD treatment due to inability to tolerate psychotherapy (e.g. due to persistent "over-engagement") or psychopharmacology due to treatment-emergent side effects would not be excluded. Subjects would also 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. They must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA. Subjects will be recruited through printed ads, Internet ads, referrals from other psychiatrists, psychotherapists, or physicians, and through word of mouth. Twelve subjects who meet all inclusion criteria without meeting any exclusion criteria will be admitted to the study. Only IRB-approved recruitment materials and advertisements will be used for the study.

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. Subjects 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 treatment-resistant PTSD, who were unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology or who discontinued treatment due to either:
    a. Inability to tolerate psychotherapy for PTSD (e.g. persistent "over-engagement" when attempting Prolonged Exposure Therapy);
    b. Inability to tolerate psychopharmacology for PTSD due to treatment-emergent side effects;
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 Stage 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. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for 10 days after each experimental session. 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 refrain from taking, for one week preceding each experimental session:
    a. Any herbal supplement (except with prior approval of the research team);
    b. Any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team);
    c. 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 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 two hours before and six 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 provide a contact (relative, spouse, close friend or other caregiver) who is willing and able to be reached by investigators in the event of a subject becoming suicidal;
18. Agree to inform the investigators within 48 hours of any planned medical interventions;
19. Are willing to refrain from participating in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period;

20. 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 during the treatment period;
21. Are proficient in speaking and reading English;
22. 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);
6. Have evidence or history of liver disease;
7. Have 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, as determined through psychiatric interview, responses to CSSRS and through clinical judgment of the investigator, 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 in the last ten years or at least once within six months of the MDMA session;
12. Require ongoing concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs;
13. Meet DSM-IV criteria for substance abuse or dependence for any substance in the past 60 days save caffeine or nicotine;
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, safety, and process measures will be used in the study. Investigators will follow the most recent version of the treatment manual in all matters relating to the psychotherapy sessions and follow-up. All psychotherapy sessions, including experimental sessions, will be recorded to audio and video, with all recordings preserved for research and training purposes.

5.1.1 Outcome Measures

The primary outcome measure will be the CAPS, a clinician-administered measure for PTSD diagnosis and assessment of symptom intensity and frequency. A qualified, blinded IR will perform the CAPS at baseline and outcome measurement timepoints. The IR will not be present during the subject's experimental sessions nor have any information regarding the experimental sessions. Subjects will be instructed not to inform the IR of 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 [101, 102].

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 [103]. Items addressing elements of the traumatic event and life function are answered as either present or not present (Yes or No). The 17 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 have a moderate to good correlation with SCID diagnosis, with kappa = 0.65 [103]. Subjects will complete the PDS questionnaire at baseline, after each experimental session, and the end of Stage 1 or Stage 2, as specified in the Time and Events Table.

The BDI-II is a 1996 revision of the BDI, a 21-item self-report measure [104, 105], that will serve as a measure of depression according to DSM-IV criteria [106]. 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 [106]. 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. Subjects will complete the BDI-II at the same times as the CAPS.

The 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 0 reflecting serious risk of causing harm to the self or others. The GAF is a reliable, validated measure of social functioning [107]. Subjects will complete the GAF at the same time as the CAPS.

The PSQI is a measure of self-reported sleep quality over a one-month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. It consists of 19 items, with possible responses ranging from 0 to 4 on a five-point scale [108]. 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 10 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 [108, 109]. Global scores correlate with other measures of alertness and self-reported sleep quality [110]. Subjects will complete the PSQI at the same time as the CAPS.

The DES-II is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual's thoughts, feelings, or experiences into the stream of consciousness or memory [111, 112]. It is an established measure of dissociative symptoms. The scale consists of statements describing facets of dissociation. Respondents indicate how often the specific experience happens to them, from "never" to "always." Responses on the original scale were made via visual analog scales. The DES-II uses the same items but with responses made on a ten-point scale from "0%" to "100%" of the time. The scale is scored by treating percentages as single digits to produce a total score. The DES-II can also be used to produce scores for three factors, amnesia, depersonalization, and derealization. The scale differentiated between respondents without psychiatric disorders or with psychiatric disorders with few dissociative symptoms and respondents with psychiatric disorders associated with dissociative symptoms [111]. Reliability of the DES-II is high (ranging from 0.79 to 0.96 in an early review), and a reported Cronbach's alpha of 0.95 [112, 113]. There may be a relationship between experiencing dissociation and occurrence of chronic PTSD [112, 114].

The SOCQ is a 100-item questionnaire based on the "Peak Experience Profile" designed by Pahnke and colleagues [115, 116]. Subjects respond to the SOCQ using a six-point Likert-type scale anchored at 0=none at all and 5=extreme (more than ever before in my life). It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. The measure is a self-report instrument and takes approximately 20 to 30 minutes to

complete. Subjects will complete the SOCQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day.

The long-term follow-up questionnaire has been developed internally by the Sponsor to assess long-term benefits and harms of MDMA-assisted psychotherapy at the long-term follow-up visit.

5.1.2 Safety Measures

Safety measures will be applied as described below to minimize risks associated with drug-assisted psychotherapy sessions. The therapists or study physician will be available via mobile phone or pager throughout the study to ensure subject safety. The therapists will maintain Basic Life Support (BLS) certification.

Safety measures, including 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 the SUD scale, which is a single-item self-report scale. The SUD will be completed repeatedly during the experimental sessions, with the degree of distress marked along seven points. Results of the SUD are intended to assist therapists in maintaining subject safety during experimental sessions.

The therapists will assess general wellbeing during each preparatory session, on each integrative session and during telephone calls for seven days. Results of this scale are intended to assist therapists in maintaining subject safety throughout the study.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [117]. 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 the therapists observe an increase in suicidality. C-SSRS data from the second integrative session after each experimental session will be kept with the subject's source record.

Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure and heart rate will be assessed periodically during each experimental session by an automatic blood pressure (BP) and pulse monitor. Blood pressure and pulse will be measured at the outset of the experimental session, and once approximately every 30 minutes for the first four hours of the experimental session, and once every hour, or as needed, thereafter. 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.

A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain [118-120]. The Changes in Tinnitus and/or Pain visual analog scale will allow rating of symptom severity from "None" to "Worst Case Imaginable". This exploratory measure will enable quantification of subjective somatic symptoms that are known to be associated with PTSD [119, 121-123]. Presence of chronic pain is associated with PTSD, possibly as a result of psychological response to traumatic stress as reflected in brain activity, such as increased amygdalar activity in response to pain and transmitter systems involved in the stress response [119, 122, 123].

All AEs and spontaneously reported reactions will be collected, as described in Section 8.5. AEs and spontaneously reported reactions may be collected during face-to-face visits or over the telephone. Common 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.

5.1.3 Process Measures

All psychotherapy sessions, including experimental sessions, will be recorded to audio and video, with all recordings preserved for research and training purposes.

Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze video data from selected preparatory, experimental and integrative sessions. The elements included in adherence criteria are specific to each type of session. These ratings will be collected, at minimum, for each therapist team in the study. The goal of these ratings will be to correlate therapist adherence to the treatment manual with outcome as a part of the sponsor's ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.

Therapeutic alliance will be assessed using the S-WAI-O on video data from selected preparatory, experimental and integrative sessions [124]. The S-WAI-O is an observer-based measure designed to assess changes in working alliance over the course of a session. The scale can provide two scores, one measuring the bond between the subject and therapist and the other measuring their agreement on tasks of therapy. These ratings will be collected, at minimum, for each therapist team in the study. The goal of these ratings will be to correlate overall S-WAI-O scores of therapeutic alliance with outcome, as measured by CAPS scores.

Questions regarding the belief of condition assignment and certainty of the belief will be asked of the therapists and subjects at the integrative session on the day after each

blinded experimental session in Stage 1. Each therapist responsible for treating the subject will indicate their belief of condition assignment and certainty based on the full dose (125mg) and comparator dose ([redacted]) groups. In line with informed consent obfuscation, where the comparator dose is not revealed, subjects will initially be asked if they believe they received MDMA or not during this assessment. If they believe they received MDMA, they will be asked about what dose they think they received. These beliefs are collected as a part of the sponsor's ongoing initiative to optimize the double-blind as a part of dose response studies.

Perception of the value of the third experimental session will be collected from each subject at baseline, and again from those receiving full dose MDMA in a third open-label experimental session in either Stage 1 or Stage 2. Expectations will be collected at baseline, at the endpoint visit with the therapists prior, and two months after the third experimental session. These perceptions are collected as a part of the sponsor's ongoing initiative to assess the therapeutic value of the third experimental session.

The Reactions to Research Participation Questionnaire (RRPQ) [125] 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 two-month follow-up, with exact time of completion varying in accordance with participation in the third open-label experimental session in Stage 1 or in Stage 2. The RRPQ is intended to assess the subject's experience as a research subject, perceived reasons for consenting to be a research subject and perceived freedom to take part in the study.

5.2 Study Procedures, Visit Descriptions, and Adherence

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

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

Prospective subjects will be prescreened by telephone according to an IRB-approved script to learn if they meet basic eligibility criteria. All individuals who are prescreened 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.

Upon signing the IRB-approved informed consent form (ICF), the potential subject may commence study-related screening activities. The screening number should also be recorded on the signed ICF. 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 should be complete by up to two months prior to enrollment. If, after reviewing all information, the investigators conclude that a subject is eligible, they will enroll the subject in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

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. 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 treatment period of the study.
d. Collect perceptions of the third experimental session.
e. The study physician will obtain medical and psychological history by interview.
f. Tinnitus and chronic pain symptom severity will be collected using a visual analog scale in subjects with a medical history of these conditions.
g. The study physician will collect information on pre-study and current medications.
h. The study 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.
    - Thyroid stimulating hormone (TSH), free T3 and free T4.
    - Human Immunodeficiency Virus (HIV) serology.
    - Urine-dip pregnancy test on females with childbearing potential.
    - Urinary drug test.
    - C-SSRS to assess suicide risk.

Results of HIV serology will be kept confidential, and appropriate referral for counseling may be necessary in accordance with state law. 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 study physician will request a review of subject medical records and request additional tests or assessments as indicated.

A blinded IR who will not be present during any of the therapy sessions will administer:

- Structured Clinical Interview for Diagnoses I Research Version (SCID-I-RV) to assess eligibility based on Axis I diagnoses, which includes a self-report questionnaire to focus on modules to use based on symptoms.
- CAPS to assess PTSD symptoms and eligibility, which may be recorded to video in as many instances as necessary to establish inter-rater reliability.
- PDS to assess self-reported PTSD symptoms.
- BDI-II to assess depression symptoms.
- GAF to assess general psychological function.
- PSQI to assess sleep quality.
- DES-II to assess dissociation symptoms.

5.2.2 Preparatory Psychotherapy Sessions - Visits 1, 2, 3 (Stage 1), 18 (Stage 2)

Subjects who do not complete all screening activities will not be enrolled. Eligibility may be discussed by phone after screening is complete and at the time Visit 1 is scheduled but the final confirmation will occur at Visit 1. If all inclusion criteria and no exclusion criteria are met, eligibility will be confirmed with the subject.

a. Complete a final review of Inclusion/exclusion criteria.
b. Assess general wellbeing.
c. Confirm eligibility and willingness to participate in study.
d. Enroll subject and issue subject number.
e. Ensure medical history and medication history is complete. After enrollment new events will be collected as AEs and new medications, as described in Sections 8.5 and 9.0.
f. Discuss medication tapering, if applicable. Upon confirmation of eligibility, the study physician will consult the prescribing physician to initiate medication tapering for subjects who must refrain from taking a psychiatric medication for the study. Tapering will follow a time course appropriate for the medication given its half-life, with the first experimental session scheduled to occur after complete washout.

The subjects will undergo three preparatory sessions lasting 90 minutes with their therapist team, prior to their first experimental session. The first preparatory session will take place at Visit 1 after enrollment confirmation. In Stage 2 (for comparator dose crossover subjects) only one preparatory session will take place prior to their first full dose open-label experimental session, as described in the Time and Events Table.

Adherence criteria for preparatory sessions should be completed as a part of one of the three sessions. These elements do not have to be accomplished in any specific order or in every preparatory session. Generally, adherence criteria for these sessions include that the therapists will work with the subject to prepare for MDMA-assisted psychotherapy. The therapists and subject will seek to form a strong working relationship with each other, and they will help the subject prepare for upcoming experimental sessions. Preparatory

sessions will promote a safe set and setting for confronting trauma-related memories, emotions, and thoughts, which is intended to develop therapeutic alliance.

During the preparatory sessions:

a. Therapists will record all sessions to audio and video. Subjects may receive copies of audio or video recordings from these sessions upon request.
b. Collect AEs and Medications, as described in Sections 8.5 and 9.0.
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 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 treatment manual.
e. 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.
f. If a subject would like a companion 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 companion.
g. The therapists will administer 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 prior to the first experimental session.
h. Assess general wellbeing at each preparatory session.
i. During the third and last preparatory session, give the Reminder of Study Rules to the subject, which includes instructions and restrictions for conduct prior to receiving the drug. Subjects must agree to:
    - Ingest only alcohol-free liquids after 24:00 (midnight) the evening before the experimental session.
    - Refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session.
    - Not use caffeine or nicotine for two hour before and six hours after ingesting the drug, or until therapists deem it safe to do so.

5.2.3 Experimental Sessions - Visits 4, 8 (Stage 1), 13, (Full Dose Group Stage 1), 19 23, 28 (Stage 2)

Subjects in Stage 1 will receive two experimental sessions of MDMA-assisted psychotherapy blinded with respect to dose, scheduled approximately three to five weeks apart. Subjects in the open-label third experimental session in Stage 1 and open-label Stage 2 will receive 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 dose of the drug received will be the same.

Adherence criteria for experimental sessions should be completed as a part of each experimental session. These elements do not have to be accomplished in any specific order. Generally, adherence criteria for these sessions include that the therapists will create and communicate a setting of safety and support the subject during periods of inner focus. Therapists will use a largely nondirective approach, following the lead of the subject's inner healing intelligence. Therapists will provide encouragement for staying present with difficult experiences. Therapists may occasionally offer gentle guidance or redirection as a choice to encourage collaborative exploration if the subject repeatedly avoids trauma related material. Therapists will inquire about somatic symptoms and if necessary encourage release of tension through movement, in whatever way feels appropriate to the subject. Therapists will use music to support the experience without being intrusive.

Table 4. **Schedule of Procedures 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, SUD
9:55	2nd Baseline BP, Pulse, Body Temperature (BT), SUD
10:00	**MDMA Administration**, begin video recording
10:30	BP, Pulse
11:00	BP, Pulse, SUD, BT
11:30	BP, Pulse; **Administer optional supplemental dose**
12:00	BP, Pulse, BT
12:30	BP, Pulse, SUD
13:00	BP, Pulse
13:30	BP, Pulse, BT
14:00	BP, Pulse, SUD
Every hour and as needed	BP, Pulse
Every 60-90 minutes	SUD, BT
Approximately six hours after drug administration	C-SSRS, General Wellbeing

Pre-drug:

a. At least 24 hours prior to the first experimental session the subject will be randomized. The study physician will obtain the container assignment using a web-based randomization program prior to the blinded sessions.
b. On the day of the experimental session, the subject will arrive approximately 60 to 90 minutes 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 they 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 therapists will administer the C-SSRS prior to drug administration.
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 two hours before or six hours after the dose of drug.
m. Subject body temperature will be measured at baseline 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^{o}C above baseline.
n. Subjects will complete the SUD at baseline 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 at baseline prior to 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 more frequently 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.

During:

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 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 as described in the treatment manual.
s. Record any spontaneously reported reactions during the session.
t. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
u. Provide water and electrolyte containing fluids throughout the session but not to exceed 3L overall.
v. A supplemental dose half the size of the initial dose will be administered approximately 1.5 to 2.5 hours after the initial dose unless contraindicated.
w. Provide food during the latter part of the session.
x. If there is a companion 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. Alternatively, the support person may arrive after the session has ended.
y. 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 treatment manual. The C-SSRS is required at least once during the session; it is preferable to administer it towards the end of the session at about six hours after the initial dose.
z. End the session if all medical and psychiatric parameters are acceptable and the subject is alert, ambulatory, and emotionally stable.

Post-drug:

aa. Give the subject the SOCQ to be completed after the end of the experimental session and prior to leaving the treatment facility the next day.
bb. The therapists will depart the site when they have concluded that the subject is emotionally and medically stable. Therapists or the study physician shall remain available to subjects during the experimental session and for one week after via 24-hour cellular phone for integration as needed.
cc. Spontaneously reported reactions, AEs, and Medications will be collected, as described in Sections 8.5 and 9.0.

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 condition 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, 9 (Stage 1), 14 (Full Dose Group Stage 1), 20, 24, 29 (Stage 2)

On the morning after each experimental session, both of the therapists from the subject's team will meet with the subject during a 60 to 90-minute integrative therapy session.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or all in each and every integrative session. Generally, adherence criteria for these sessions include discussing material that emerged during experimental sessions and helping subjects integrate their experiences both internally and into daily life. Therapists will validate the choices of the subject about how much they wish to communicate their thoughts, feelings and experiences at this time, but will elicit enough information to be able to assess the subject's level of emotional stability and state of emotional and physical wellbeing. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone for additional meetings if needed. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

During integrative psychotherapy sessions:

a. The integrative psychotherapy session will be recorded to audio and video. Subjects may receive copies of this session upon request.
b. The therapists will administer the C-SSRS during each integrative session.
c. Prior to integrative psychotherapy, the subject and both therapists will indicate their beliefs concerning subject condition assignment.
d. Discuss and review events that occurred with the subject during the experimental 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.

e. The therapists will remain accessible any time the subject needs support outside the scheduled integration sessions.
f. Assess the subject's mental health and the presence of any remaining reactions during integrative psychotherapy immediately after each experimental session.
g. 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.
h. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
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, AEs and Medications will be collected, as described in Sections 8.5 and 9.0.
k. Remind the subjects that they will have daily phone contact for the next seven days.

5.2.5 Daily Telephone Contact for Seven Days after an Experimental Session

During daily phone contact:

a. Investigators will follow the most recent version of the treatment manual in all matters relating to follow-up subsequent to the experimental psychotherapy sessions.
b. 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. The goal of daily contact is assessment of changes in general wellbeing, safety of the subjects, and offering support for subjects.
c. The telephone contact will be for a brief check-in lasting five 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.
d. On the second and seventh day of contact after the experimental session, the therapists will administer the C-SSRS.
e. General wellbeing will be assessed at each phone call.
f. Spontaneously reported reactions, AEs and Medications will be collected, as described in Sections 8.5 and 9.0.

5.2.6 Integrative Psychotherapy Between Experimental Sessions - Visits 6, 7, 10, 11, (Stage 1), 15, 16, (Full Dose Group Stage 1), 21, 22, 25, 26, 30, 31 (Stage 2)

In addition to the session the morning after each experimental session, the subject will have two additional integrative psychotherapy sessions with the therapists lasting 90 minutes with the therapists between each experimental session and in the month following the last experimental session. The therapists may conduct more sessions if they and the subject deem it necessary.

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

During integrative psychotherapy sessions:

a. Record each integrative session to audio and video. Subjects may receive a copy of one or more integrative sessions upon request.
b. The C-SSRS will be administered just prior to beginning each integrative session.
c. General wellbeing will be assessed at each integrative session.
d. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
e. The subject will complete the PDS questionnaire after each experimental session on the third integrative session or primary endpoint (after the second experimental session only), according to the Time and Events Table.
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. Collect AEs and medications, as described in Sections 8.5 and 9.0.
i. NOTE: If an integrative session falls within the period of telephone contact and additional phone call is not required that day, all data normally collected during the telephone call will be completed in person.

5.2.7 Evaluation at Primary Endpoint and Unblinding - Visit 12 (Stage 1)

The primary endpoint evaluation in Stage 1 will occur one month (within a window of plus or minus two weeks) after the second blinded experimental session. This visit will consist of two meetings that may be completed on separate days, one with the IR and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point one month after their last experimental session.

At the primary endpoint:

a. Subjects will meet the IR for at least an hour and a half.
b. The blinded IR will administer:
    - CAPS to assess PTSD symptoms, which may be recorded to video in as many instances as necessary to establish inter-rater reliability.
    - PDS to assess self-reported PTSD symptoms.
    - BDI-II to assess depression symptoms.
    - GAF to assess general psychological function.
    - PSQI to assess sleep quality.
    - DES-II to assess dissociation symptoms.
c. After completing all assessments and measures with the IR, 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 visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
g. The blind will be broken for the subject's condition assignment. Only the IR will remain blind to condition assignment at this time.
h. If the subject was assigned to receive comparator dose MDMA, the therapists will discuss enrollment in Stage 2 (see Section 5.2.9). Comparator dose subjects will not complete the third experimental session and associated integrative sessions in Stage 1.
i. Collect perceptions of the third experimental session from full dose subjects.
j. If the subject was assigned to receive full dose MDMA, the subject will complete a third open-label experimental session, with associated daily phone calls and integrative sessions in Stage 1 (see Sections 5.2.3-6).

5.2.8 End of Stage 1 - Visit 17 (Full Dose Group Stage 1)

Full dose subjects will repeat all outcome measures with the IR and meet with the therapists again two months (within a window of plus or minus two weeks) after their final open-label experimental session, which will be the final visit in Stage 1 (see Section 5.2.7). This visit will consist of two meetings that may be completed on separate days, one with the IR and the other with the therapists.

At the end of Stage 1:

a. Full dose subjects who complete Stage 1 and comparator dose subjects who elect not to participate in Stage 2 will complete the RRPQ and continue on to the long-term follow-up visit.
b. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
c. Subjects who will continue on to the long-term follow-up may return to taking psychiatric medications after the end of Stage 1 if necessary.
d. Subjects who will continue on the long-term follow-up will receive a memory aid card for use between their end of Stage 1 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.
e. Collect AEs and medications, as described in Sections 8.5 and 9.0.

5.2.9 Open-label Stage 2 (Comparator Dose Subjects from Stage 1)

During Stage 2:

a. Subjects will be reminded that participation in Stage 2 is voluntary and optional.
b. Subjects who elect to cross over to Stage 2 will undergo the same course of therapy and evaluation as in Stage 1, but with full dose MDMA during three experimental sessions.
c. Assessment of PTSD symptoms at the primary endpoint will serve as baseline assessments in Stage 2.
d. If the start of Stage 2 is delayed for more than 30 days from the primary endpoint (Visit 12) to the first preparatory session in Stage 2 (Visit 18), the IR will re-administer the CAPS, PDS, BDI-II, GAF, PSQI, and DES-II and these scores will be used as the baseline for comparison to assessment at the secondary endpoint and the end of Stage 2.
e. Subjects entering Stage 2 will meet with both therapists for a single preparatory psychotherapy session.
f. Subjects will have the same sequence of experimental sessions and integrative therapy as full dose subjects in Stage 1 in an open-label context (e.g. without unblinding). Visits will be scheduled consecutively according to the Time and Events Table.
g. The same outcome measures completed by full dose subjects in Stage 1 will be administered during Stage 2.
h. The same safety measures as those in Stage 1 will be administered during Stage 2.
i. The end of Stage 2 will be completed in the same manner as the end of Stage 1 (see Section 5.2.8).
j. Investigators will follow the most recent treatment manual in all matters relating to the Open-Label Stage 2 experimental psychotherapy sessions.

5.2.10 Long-term Follow-up

All subjects will be evaluated for long-term effects 12 months (within a visit window of plus or minus one month) after their last MDMA-assisted psychotherapy session. This visit will consist of two meetings, one with the IR and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point.

At the long-term follow-up visit:

a. The IR will administer the CAPS, PDS, BDI-II, GAF, PSQI, and DES-II.
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.
c. Subjects will complete a questionnaire and answer questions assessing positive and negative long-term effects of the study. This session may be video recorded.
d. The therapists will assess suicidality with the C-SSRS.
e. General wellbeing will be assessed.
f. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
g. 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 “S001”. 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 “12” 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 12001, second 12002, etc.

In total, 12 subjects will be enrolled into the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions. An unblinded randomization monitor will generate the randomization list. Subjects will be assigned subject numbers, 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 primary endpoint per protocol via the web-based randomization program. Detailed instructions will be provided to the site in a separate document.

If there is an emergency requiring knowledge of subject's condition assignment, the blind may be broken for an individual subject. The investigator may be provided with the condition assignment in case of emergency through the web-based randomization system.

5.4 Removal of Subjects from the Study

Subjects can withdraw consent at any time without prejudice. The therapists can withdraw a subject if, in their clinical judgment, it is in the best interest of the subject or if the subject cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If the therapists withdraw a subject from the study, the therapists will explain the reason for withdrawing the subject. The reason for early termination will be recorded in the subject's source records and CRF.

If a subject develops any exclusion criteria that in the opinion of the Medical Monitor, affects the safety of the subject, including psychiatric diagnosis, pregnancy or excluded medications, the subject will discontinue treatment but remain in the study for follow-up purposes. Whenever possible, the tests and evaluations listed for the primary endpoint and 12-month follow-up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the investigators, Medical Monitor and/or Sponsor.

Subjects who discontinue treatment prior to the primary endpoint will be replaced. Individuals who replace these subjects will be assigned the next available subject number. Subjects who discontinue treatment after the primary endpoint in Stage 1 will not be replaced. If Stage 1 subjects discontinue treatment before the primary endpoint, the site should contact the randomization monitor for replacement instructions. Detailed instructions will be provided to the site in a separate document.

5.5 Premature Discontinuation of the Study

The Sponsor or the lead Clinical 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 state regulations.

6.0 Investigational Product

6.1 Description of Active Compounds

The investigational product 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 [126-128]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower. See Section 2.2.3 and the IB for more information on the investigational product.

6.2 Preparation and Administration

In this study, 12 subjects will be randomized to the two conditions described in Table 5 (below). The blind will be broken for each subject after the primary endpoint is completed. The subjects who received the comparator dose of MDMA 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
7	Full Dose	Blinded	125 mg	62.5 mg	187.5 mg
5	Comparator Dose	Blinded	[redacted]	[redacted]	[redacted]
5 or less	Stage 2	Open-label	125 mg	62.5 mg	187.5 mg

6.2.2 Compounding

MDMA in bulk will be sent from a Schedule 1 licensed storage facility to the Drug Enforcement Agency (DEA) Schedule I license holder for the study. The Schedule I license holder and unblinded randomization monitor will oversee compounding by a pharmacist in a manner that will maintain the blind for the Schedule I license holder. The pharmacist will provide bulk lactose for compounding MDMA capsules. The pharmacist will weigh the MDMA into doses of 125 mg, 62.5 mg, [redacted] and [redacted] (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules with lactose. Capsules for the initial dose will be clearly differentiated from capsules used for the supplemental dose. All capsules will be compounded so that they weigh the same amount, but contain varying amounts of MDMA and lactose.

6.2.3 Labeling

The initial 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 federal and state regulations.

Box Label
MAPS Study# XXXX Investigational Product: MDMA Dose: Blinded ([redacted] [redacted] OR 125 mg, 62.5 mg) Lot #: XXXXX Administer as per protocol Caution-Limited by Law to Investigational Use Only

Container Label	Container Label
MAPS Study # XXX Container # XXX Subject #_____ Session#_____ Stage 1 MDMA Administer as per protocol Investigational Use Only	MAPS Study # XXX Container # XXX Subject #_____ Session#_____ 125 mg & 62.5 mg 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 experimental session.

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 I compound and will be stored and handled in compliance with all relevant federal and state regulations. In accordance with these requirements, the Schedule I license holder will be responsible for storing, dispensing, and administering the MDMA. It will be stored in a secure safe in accordance with federal and state regulations.

Investigational product will only be removed from the safe for one subject at a time at the time of the session and the MDMA will not leave the control of the Schedule I license holder until consumed by the designated subject. 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 federal regulations.

6.5 MDMA Stability

Complete details on the chemistry, manufacturing, and control of the MDMA to be used are described in Drug Master file (DMF) # 6293. As described in that file, MDMA was prepared for human consumption in 1985 by David Nichols, Ph.D., at the Dept. of Medicinal Chemistry and Pharmacology, Purdue University. The identity and purity of this MDMA was confirmed using High Performance Liquid Chromatography (HPLC) in 1997 as described in DMF # 6293 and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor prior to starting MAPS' first U.S. pilot study of MDMA-assisted psychotherapy in people with PTSD. The analysis found the MDMA to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart on February, 2006, continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9% pure. This MDMA is currently in use in an ongoing investigation of MDMA-assisted psychotherapy in the U.S., was also used in MP-1 with drug administration ending in 2008, and it was also used in a non-sponsor supported study in 2006 [129].

7.0 Risks of Participation

7.1 Risks and Discomforts Associated with 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 for research and training purposes. 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 and assessing adherence to the treatment manual. 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, insomnia, 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, parasthesias (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 subjects 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 subjects in the MDMA than the placebo condition, and irritability was slightly more likely to be reported in the placebo condition. Additionally, subjects 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 IB.

MDMA may produce mild alterations in sensory perception and altered perception of time [65, 72, 130]. Women may be more sensitive to these effects [96]. MDMA acutely affects attention, information processing, and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of complex scene changes [77]. 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 sponsor's Investigator 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, peak blood pressure values were higher than 140/90 mmHg. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of subjects and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity. For more information, see the sponsor's Investigator Brochure.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing hypertension and monitoring blood pressure and pulse, as described in 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 neurological symptoms or other potential indicators of hypertension will have more frequent measurements and assessment by the study physician. Any subject who experiences medical complications during an experimental session will not be given another experimental session unless it is approved by the Clinical Investigator, study physician and the Medical Monitor.

In case of need, subjects will be transferred to the emergency room at the closest hospital, as described in Section 8.4. Reasons for moving a patient to an Emergency Department (ED) would include, but not be limited to, severe headache in the setting of hypertension, angina, or neurological deficits regardless of blood pressure. The investigators and study physician may, at any time, make a clinical judgment to transfer the patient to the ED for closer monitoring and additional treatment.

The study physician will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). The 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, and will notify the study physician if this occurs for on-site evaluation or a decision to initiate transfer to the ED. If any subject has neurological deficits, as assessed by the study physician, whether or not they are associated with hypertensive crisis, they will receive oxygen and will be monitored as described above. If necessary, they will be transported to the emergency department at the closest Hospital for further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the three-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [131, 132].

The therapists will observe the subject and note any complaints of chest pain. If a subject experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will receive heart rhythm monitoring, oxygen and will be monitored as described above. If necessary, he or she will be transported to the ED 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 subject has had an AMI, they 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 [133].

7.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported one to three days after MDMA administration [63, 96, and see the IB]. Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately three to five hours after drug administration), or even later. Anxiety or distress during the session may last for as little as five minutes or for as long as five hours or more. 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 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 six to eight 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, physician, or therapist will stay with the subject until the time of his or her appointment with the 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 study physician may prescribe a rescue medication such as a benzodiazepine, zolpidem or other anxiolytic or sedative according to the physician's clinical judgment. This medication will be captured on the concomitant medications CRF page. The physician should not prescribe an SSRI, SNRI or MAOI in this context unless it has been determined that the subject will be withdrawn from the study. 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 ED if necessary.

Subjects hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the investigators 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. For those subjects engaged in an ongoing psychotherapeutic

relationship with the investigator(s), the management of any psychiatric complications will be undertaken by them in their capacity as therapists.

7.2.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [96] 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 subject. If at any time the temperature rises more than 1.5°C above baseline despite these efforts, the study physician will be consulted for further evaluation and treatment.

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 [134, 135], as discussed in the IB.

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 treatment portion 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 [136]. 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. Meanwhile, another recently published meta-analysis has taken careful steps to overcome methodological limitations in previous work, and found only modest evidence of neurotoxicity [137]. 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 IB.

7.2.6 Risk Mitigation

Careful review of medical screening data will be utilized to exclude potential subjects with pre-existing exclusionary medical conditions from the study. Study procedures have been developed to mitigate the risks of receiving MDMA described in detail in the IB. 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 subject exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an experimental session, unless it is approved by the Clinical Investigator, study physician and the Medical Monitor.

7.3 Abuse Liability

Findings in humans and 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 IB.

Whether MDMA-assisted psychotherapy will cause PTSD patients to develop symptoms of abuse is an open question that the sponsor is addressing on an ongoing basis. Based on long-term follow-up data from two sponsor-supported studies (N=32), only one subject took Ecstasy after completing the study and failed to reproduce the experience from the study, and a number of subjects volunteered that they would never seek out Ecstasy outside a legal, controlled, therapeutic setting. In addition, negative results from MDMA-specific drug testing data obtained from the Swiss study MP-2 (N=12) supports that none of these subjects took Ecstasy outside of the study during the long-term follow-up period.

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 subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subjects' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current IB 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 study physician 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 study physician 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.

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. Each reported reaction will be followed during follow-up phone calls or visits until resolution.

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 study physician, 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 study physician, 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 private practice setting, 1.2 miles away from the Boulder Community Hospital, where emergency equipment is immediately available. The study physician will be available in the case of medical emergencies and will be three miles away from the study site during experimental sessions. The therapists or study physician will be available via mobile phone or pager throughout the study if any problem occurs when a subject is not at the site, and they will continue to see their outside therapist throughout the study. 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 IB. Similar contingency plans will be used in this protocol. The site will provide an Automated External Defibrillator (AED). The therapists will maintain BLS certification.

With these personnel and equipment, the therapists or study physician will be able to perform basic cardiac life support if necessary and call Emergency Medical Services (EMS) to transport the subject to the ED at the closest hospital. In the event of a medical emergency or any other medical problem, the study physician will be immediately available by phone, and based on his assessment of the situation, he will make the decision to either evaluate the subject himself at the site, have the therapists call EMS to transport the subject to the ED, or instruct the therapists to take the subject to the ED where he will meet them.

8.5 Adverse Event Collection

The study physician will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The therapists will collect AEs during study visits after enrollment.

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 study physician, Clinical Investigator (CI), or designee should call the CRA during normal working hours and verbally inform the CRA of the SAE. During off business 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
[redacted]

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 subject termination.
- All AEs 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 enrollment through the subject's last two-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 follow-up period between the end of Stage 1/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

The study physician will record concomitant medications 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 study physician 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 five times the particular drug's half-life).

The therapists will request information about any changes in medication just prior to each experimental session. The study physician will be responsible for reviewing and confirming all medications collected during the study.

All medications, over the counter (OTC) and prescription will be collected from screening through seven days after the last MDMA session. From seven 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 described 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. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for 10 days after each experimental session.

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

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 end of Stage1/Stage 2 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 and discontinue birth control after the final two-month assessment if necessary.

10.0 Clinical Laboratory Assessments

The study physician will examine laboratory assessments gathered in screening for assessing subject eligibility. The study physician will use a list of normal ranges to conclude whether subjects are eligible for the protocol, and will indicate justification for admitting subjects with abnormal values, after consultation with the medical monitor.

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

- Serum electrolytes and metabolic profile.
  - 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.
  - Hematocrit
  - Hemoglobin
  - MCV
  - MCH
  - MCHC
  - RDW
  - Percentage and absolute differential counts
  - RBC
  - Red blood cell count
  - White blood cell count
- Urinalysis.
  - Color
  - Appearance
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Occult blood
  - Leukocyte esterase
  - Nitrite
  - Bilirubin
  - Urobilinogen
- Thyroid function.
  - TSH high sensitivity
  - Free T4

  - Free T3
- HIV serology.
- Urine-dip pregnancy test for females of childbearing potential.
- Urinary drug test will be performed.

The laboratory that will perform assessments other than the urine drug screen and pregnancy test is:

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. From the start of the study, videos from selected sessions will be reviewed for adherence to the treatment manual, therapeutic alliance, and inter-rater reliability. Adherence will be checked by monitoring and by review of selected video 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.

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 judge the clinical and statistical significance of the study based on a comparison of observer-blind data collected at baseline and the primary endpoint using the primary outcome measure, which is the CAPS. Descriptive statistics will be computed overall and within the two dose conditions for all available data from outcome measures, including minimum, maximum, average, and standard deviation. 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 full dose MDMA and comparator 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.

The Sponsor will examine full dose and comparator dose groups for homogeneity through comparing demographic characteristics. 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 Sponsor will examine CAPS, PDS, BDI-II, GAF, PSQI, and DES-II scores at baseline and the primary endpoint in full dose and comparator dose conditions using difference scores, and independent sample t-tests will be used to test for significance between groups, with p value set at 0.05.

A repeated measures analysis of variance (ANOVA) will be performed upon PDS scores at baseline, after each experimental session, and at the end of Stage 1, with p value set at 0.05. Condition will serve as a between-subjects factor. Results of ANOVA analysis will be used to examine the effects of each experimental session on self-reported PTSD symptom severity. PDS and CAPS scores will be correlated via Pearson's product moment correlation at baseline and the primary endpoint to provide a comparison of a self-report measure with a clinician-administered measure of PTSD symptoms.

The sponsor will compute descriptive statistics for SOCQ scores from after each MDMA-assisted psychotherapy session, and SOCQ scores will be compared across the full dose and comparator dose conditions for the blinded experimental sessions, in the full dose condition after the third Stage 1 experimental session and in all Stage 2 experimental sessions. The data will be explored for effects of condition on domain scores in the SOCQ.

Changes in PTSD symptoms, symptoms of depression, self-reported sleep quality, and global functioning at the primary endpoint will be compared with scores occurring two months after the third Stage 1 session, with p value set at 0.05 to see whether a third session produces further decline in symptoms.

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

Formal statistical comparisons between Stage 1 and Stage 2 scores may only occur if, at minimum, three subjects complete Stage 2. Data from the open-label third experimental session in Stage 1 will be compared statistically to Stage 2 data, and data from this session will only be utilized if they are equivalent to Stage 2 data. The sponsor will perform an analysis comparing CAPS and PDS scores after experimental and open-label sessions for subjects in the full dose condition and a separate analysis for subjects enrolled in Stage 2.

Perception of the third experimental session will be examined at baseline, during Stage 1 and Stage 2, before and after subjects have undergone a third experimental session. The results of this analysis will inform the sponsor of expectancies and the value of the third session for future protocol development. These data will be correlated with primary/secondary endpoint CAPS data compared to end of Stage 1/Stage 2 CAPS data.

The sponsor will examine CAPS, PDS, GAF, BDI-II, PSQI, and DES-II, scores 12 months after the final MDMA-assisted psychotherapy session. If there is enough data available for formal comparisons, the Sponsor will use repeated measures ANOVA with baseline, end of Stage 1/Stage 2 and 12-month follow-up scores at p value set at 0.05.

The sponsor will collect ratings of adherence to the treatment manual across a selected number of sessions of different types. Descriptive statistics will be computed for each adherence scale within a given session. The sponsor will examine the factor structure of the measures of adherence to assist in further development of adherence and competence measures. The sponsor will correlate the adherence ratings with Global CAPS scores to investigate the effects of adherence to the treatment manual on reduction in PTSD symptoms.

Descriptive statistics will be computed on average overall S-WAI-O scores across a selected number of sessions of different types. The sponsor will explore the structure of a cross-session S-WAI-O score representing average overall scores via factor analyses. Average overall S-WAI-O scores of selected sessions will be correlated with Global CAPS scores in each stage of the study, as applicable.

Subjects who discontinue treatment prior to the primary endpoint will be asked to complete an outcome assessment prior to continuing to the long-term follow-up. The data from these subjects will be tested for equivalence to data from subjects completing the study per protocol. If found to be equivalent, data from these subjects will be presented as an exploratory analysis to examine results without bias towards subjects more likely to complete the study per protocol.

The therapists will record average baseline and peak and post-drug blood pressure, heart rate and body temperature for subjects 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 compare peak blood pressure, heart rate, and body temperature for subjects after sessions with full dose MDMA or

comparator dose MDMA whenever possible. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

An interim analysis may be completed when all subjects have completed Stage 1 and Stage 2, but not all subjects have completed the 12-month follow-up evaluation. Additionally, an interim analysis may be performed after all subjects have completed Stage 1 but not necessarily before all eligible subjects complete Stage 2. This analysis will address safety, efficacy and process measures. Results of the interim analysis will have no effect on study conduct.

12.1 Statistical Power

This is a pilot study intended to collect estimates of effect size of full dose MDMA (125 mg) versus comparator dose MDMA ([redacted]). 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 U.S. 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 [71]. The estimated effect size for this study may be lower as a result of comparing the full dose of MDMA with the comparator 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 to calculate estimated statistical power for the primary outcome measure of this study, assuming an effect size of 0.8 for the impact of two sessions of MDMA-assisted psychotherapy on symptoms of PTSD [138], reducing the effect size to account for the hypothesized effects of using a comparator dose of [redacted] that is higher than the [redacted] dose employed as an active placebo in a sponsor-supported study. The software calculated an estimated power of 0.24, 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 0.4. Statistical power estimates were not available for secondary and exploratory measures, as they were previously not used in sponsor-supported studies.

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 ICF must be reviewed and approved by a properly constituted IRB and FDA before study start. Signed and dated documentation of IRB and FDA approvals 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 main licensed therapists are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. Information about the study must be given orally and in an understandable form. Written information about the trial will also be provided. The informed consent discussion must be conducted by a person who is qualified according to FDA regulations. The subject should have the opportunity to inquire about details of the MDMA-assisted session and to consider participation.

The ICF will state the probability of random assignment to the full dose group or the comparator dose group, however there will be a level of obfuscation, which makes it unclear that there is only one comparator dose of [redacted] of MDMA. The ICF will indicate the comparator dose may or may not contain MDMA. If subjects ask about the composition of investigational product in the comparator dose group, the exact contents of the comparator dose will be said to include lactose and may or may not include MDMA, however everyone assigned to the comparator dose group will have the opportunity to receive full dose MDMA during Stage 2. For all subjects in the comparator dose group, the content of the comparator dose will be disclosed after the primary endpoint visit when unblinding occurs. Unblinding and debriefing at the primary endpoint will take place with the co-therapist team and the subject. During the debriefing, subjects will be informed of the contents of the investigational product they received during the blinded experimental sessions in Stage 1 and the contents of investigational product will be fully disclosed.

In addition to the explanation of study visits, the information should include that access to original medical records and processing of coded personal information must be authorized. Written consent to take part in the study includes giving the investigators permission to view the subject's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

Eligible subjects may only be included in the study after signing the IRB approved ICF. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol, including screening activities). 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 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 ICF and written information should receive approval

from an IRB before use. The subject should be informed in a timely manner if new information becomes available that might affect the decision to take part in the MDMA-assisted session. The communication of this information should be documented.

Subjects can withdraw consent at any time without prejudice. If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the investigators will have full access to the subject's medical records, including termination visit information. If a subject revokes only the HIPAA authorization, the investigators will have full access to all of the subject's medical records prior to the date and time of revocation.

15.0 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of subjects in their role as research subjects. 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. Except for the screening log, the ICF, and a subject contact information sheet that will be stored separately from other documents, all data will be identified only by the subject's initials on the source document and four-digit subject number. If past medical records are needed, subjects will sign forms for the release of information upon consent to permit screening for protocol enrollment. Copies of audio and video recordings intended for sharing with subjects will only be marked with the subject's subject number. Any materials mailed to subjects will be sent along with stamped return envelopes using the office address of the Clinical Investigator both as main and return address. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators directly involved in the protocol, with access to data will not be provided with any information that would identify subjects by name or by other means, such as social security number.

All psychotherapy sessions will be recorded to video and audio. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted psychotherapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. CAPS assessments may also be recorded to video to establish inter-rater reliability. Full names and addresses will not appear in these recordings.

16.0 Costs to Subjects

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

17.0 Treatment and Compensation for Study Related Injury

Treatment of a study-related emergency would first be billed to a subject's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a subject's health insurance. Some study-related emergencies can be treated by the investigators, as described in Section 8.4. If the study physician cannot treat a study-related emergency, then there are contingency plans for the transport of subjects to the nearest hospital.

18.0 Record Retention

Investigators must retain all study records required by the Sponsor and applicable ICH-GCP and FDA 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.

19.0 References

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