

**INVESTIGATOR AGREEMENT AND EXTERNAL PROTOCOL SIGNATURE PAGE**

I have read the protocol titled:

“A Randomized, Double-Blind, Controlled Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada” Amendment 2 Version 3, dated June 20, 2014

I have been adequately informed about the investigational product to date. I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol.

I will ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. I will maintain a list of sub-investigators and other appropriate qualified persons to whom I have delegated significant trial-related duties.

I will not enroll the first subject in the study until I have received approval from the appropriate EC, and until all legal requirements in my country have been fulfilled.

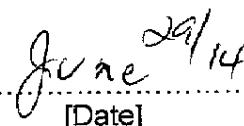
By signing this signature sheet I agree:

- to conduct this clinical study in compliance with ICH GCP, with the applicable regulatory requirement(s), and with the study protocol agreed to by the sponsor and given approval/favorable opinion by the EC or IRB
- to comply with procedures for data recording/reporting
- to permit monitoring, auditing, inspection and EC or IRB review
- to retain the study related essential documents according to legal requirements and as agreed with the sponsor

Qualified Investigator


[Investigator's Signature]

Dr. Ingrid Pacey
[Print Name]

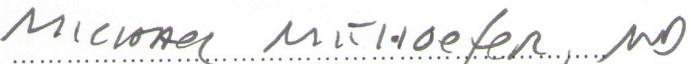

[Date]

SPONSOR AGREEMENT

This study protocol # MP-4 Amendment 2 Version 3 was subject to review and has been internally approved by the clinical study team. The information it contains is consistent with:

- The current version of the Investigator's Brochure
- The moral, ethical and scientific principles governing clinical research as set out in the Good Clinical Practice guidelines

The investigator will be supplied with details of any significant or new findings, including adverse events.

MAPS**Signatory or Medical Monitor**
[Signature]
[Date]
[Print Name]

**A Randomized, Double-Blind, Controlled Phase 2 Pilot Study of Manualized
3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects
with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada**

Amendment 2 Version 3: June 20, 2014

Study Code: MP-4

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
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Study Description: This is a Phase 2 randomized, double-blind, placebo controlled study to assess safety and efficacy of manualized MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD. Seven subjects will be randomized to receive full dose MDMA (full dose condition) and five subjects will receive a comparator dose (comparator condition), with an optional supplemental half-dose available 1.5 to 2.5 hours after the initial dose.

A team consisting of a male and female therapist will conduct psychotherapy according the treatment manual provided. There are two teams involved with this study. One team will consist of the Qualified Investigator and a co-therapist, and the second team will consist of a co-therapist and a Sub-investigator who have been delegated the authority to conduct therapy by the

Qualified Investigator. Information will be collected regarding consistency and response of these teams by reviewing adherence criteria in selected blinded videos of therapy sessions. All study procedures, including administration of the Investigational Product, will be done by the Investigator or designated qualified study personnel.

In Stage 1, all subjects will have two blinded experimental sessions of manualized MDMA-assisted psychotherapy scheduled at a three to five week interval, within a moderate course of non-drug psychotherapy (preparatory and integrative sessions), after which they will complete the primary endpoint assessment. Integrative sessions may be completed via telemedicine, telephone or in person. After the primary endpoint assessment, the subject and the therapists will be unblinded. Subjects assigned to receive full dose MDMA will receive a third open-label experimental session and complete Stage 1. Subjects assigned to receive comparator dose will have the option to cross over, without completing Stage 1, to an open-label study segment following similar procedures, referred to as Stage 2. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Stage 2 follows similar procedures and visit schedule as Stage 1 using varied active doses of MDMA, in which each initial dose may be followed by a supplemental dose that will be half of the initial dose. In Stage 2, subjects will receive an initial dose of 100 mg MDMA during the first experimental session. The co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg MDMA in the second and third experimental sessions.

A blinded Independent Rater (IR) will assess PTSD symptoms, general function, and psychological symptoms. These symptoms will be assessed at baseline, the primary endpoint, and two months after the third experimental session in Stage 1 and equivalent timepoints in Stage 2. Outcome measures after baseline may be completed via telemedicine or in person. Neurocognitive measures must be done in person. Symptoms and long-term benefits and harms will be assessed again twelve months after the final experimental session. This study will provide an estimate of effect size based on dose comparison of PTSD symptoms to MDMA-assisted psychotherapy. This study will also permit the refinement of the treatment manual through blinded review of adherence criteria assessed by rating videos of psychotherapy sessions.

Dose Selection: This study will compare the effects of psychotherapy sessions assisted by comparator dose or full dose MDMA. The comparator dose will be 0 mg MDMA followed 1.5 to 2.5 hours later by 0 mg MDMA. The full dose will be 125 mg MDMA followed 1.5 to 2.5 hours later by 62.5 mg MDMA.

Table 1. Stage 1 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose
1 and 2	Comparator Dose	0 mg	0 mg	0 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

Table 2. Stage 2 Drug Doses

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

The MDMA doses to be used in this study have been used in previous studies sponsored by MAPS. 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 is not expected to produce effects associated with MDMA.

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

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.

Primary Outcome Measure: Clinician-Administered PTSD scale (CAPS) administered by a blinded Independent Rater. With the exception of the Screening/Baseline visit this measure can be administered via telemedicine or in person.

Secondary Outcome Measures: Posttraumatic Diagnostic Scale (PDS), Global Assessment of Function (GAF), Beck Depression Inventory-II (BDI-II), Neuroticism Extroversion Openness Personality Inventory (NEO-PI), Pittsburgh Sleep Quality Index (PSQI), Posttraumatic Growth Inventory (PTGI), and Dissociation Scale II (DES-II)

Safety Measures: Columbia Suicide Severity Rating Scale (C-SSRS), Repeatable Battery for Assessment of Neuropsychological Status (RBANS), Paced Auditory Serial Addition Task (PASAT), Vital signs, Subjective Units of Distress (SUD), Adverse Events and Spontaneously Reported Reactions, Concomitant Medications, Visual analog scales assessing pain and tinnitus, in participants with medical history of chronic pain and/or tinnitus

Process Measures: Belief of condition assignment, States of Consciousness Questionnaire (SOCQ), Perceptions of Experimental Sessions, Reactions to Research Participation Questionnaire (RRPQ), Adherence to Treatment Manual

Recruitment and Subject Population: Subjects may be male or female, aged 21 or older, with a confirmed diagnosis of chronic PTSD, who have undergone at least one treatment of adequate dose/duration for PTSD without achieving remission. Prior treatment can include psychotherapeutic or pharmacological treatments, and people who have undergone one or more prior treatments are eligible for study participation. Subjects would not be excluded for having more than one traumatic event. Subjects must have a CAPS score equal to or greater than 60 and must meet all protocol inclusion criteria and no exclusion criteria at baseline. Subjects 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.

Study Procedures: After giving written informed consent, prospective subjects will be screened for eligibility, and twelve subjects meeting study criteria will be enrolled. In consultation with their prescribing physician, any individuals taking psychiatric medications will taper off these medications, allowing for a washout period of at least five times the medication half-life plus one week for stabilization before the first experimental session. Subjects taking psychostimulants for ADHD or gabapentin for pain management may continue to take these medications so long as they discontinue use for five half lives prior to each experimental session and resume use of psychostimulants ten days after an experimental session. During the study, benzodiazepines or zolpidem or other anxiolytic or sedative may be used as rescue medications if needed as approved by the qualified investigator responsible for the study. Any subjects who are in psychotherapy with an outside therapist at the time of enrollment may continue that therapy during the study without increasing the number or type of sessions or changing psychotherapists or type of psychotherapy.

Symptoms of PTSD, perceived positive changes or growth after trauma, general psychological function, depression, sleep quality and dissociative experiences will be assessed at baseline in all subjects. The RBANS and PASAT will be administered to all subjects at baseline. The CAPS interviews may be recorded to audio and video to assess reliability of CAPS ratings. The first experimental session will be preceded by three preparatory sessions and followed by three integrative psychotherapy sessions. During preparatory sessions, subjects will learn what to expect during experimental sessions, and during integrative sessions they will receive support in integrating their experiences and insights from the experimental sessions. Preparatory, experimental and integrative sessions will be audio and video recorded for research purposes. Video data will be evaluated for adherence to the therapy manual using adherence criteria ratings.

Seven subjects will be randomized to receive a full dose of MDMA and five will be randomized to receive comparator dose during two experimental psychotherapy sessions scheduled three to five weeks apart. After each experimental session, subjects will spend the night at the treatment facility with an attendant on duty. Subjects will complete the SOCQ in the time between an experimental session and the integrative session on the day after. Subjects and therapists will report their beliefs on their condition assignment at the integrative session on the day after each experimental session. There will be daily phone contact with one of the therapists for seven days after each experimental session. Throughout the study, changes in symptom severity of tinnitus and/or chronic pain will be collected as needed when subjects who have a medical history of these conditions report a change in symptoms using a simple visual analog scale. The PDS will be completed on the third integrative session after the first and third experimental sessions and during IR visits. Symptoms of PTSD, depression, sleep quality, dissociation, and perceived growth, general psychological function and cognitive function will be repeated for each subject at the primary endpoint, after which the blind will be broken. Subjects who learn they were assigned to full dose will have a third and final open-label experimental session with full dose MDMA, two months after which their psychological symptoms will be assessed again. Subjects who learn they were assigned to receive comparator dose will have the opportunity to enroll in Stage 2. Stage 2 consists of a similar series of procedures and visits except that subjects receive one preparatory visit and three open-label experimental sessions. Subjects will receive 100 mg MDMA possibly followed by 50 mg during the first open-label session. The decision to titrate the dose in the second and third experimental sessions in Stage 2 will be based on the experience of the first session. If 100mg MDMA does not seem to be the optimal therapeutic dose based on the first experimental session in Stage 2, the dosage may be increased by an increment of 25mg in order to achieve the optimal therapeutic dose. The supplemental doses for each experimental session will be half of the initial dose, respectively. Cognitive function will be assessed via RBANS and PASAT again at the primary endpoint and two months after the third Stage 1/Stage 2 experimental sessions.

There will be a long-term follow-up with repeated outcome measures for symptoms of PTSD, depression, dissociation, posttraumatic growth, sleep quality, pain and/or tinnitus, if applicable, twelve months after the subjects' final experimental session. The study therapists will maintain communication with the referring physician or therapist and any other healthcare providers requested by the subject.

Subjects discontinuing treatment prior to the primary endpoint will be replaced until complete data has been collected from twelve subjects.

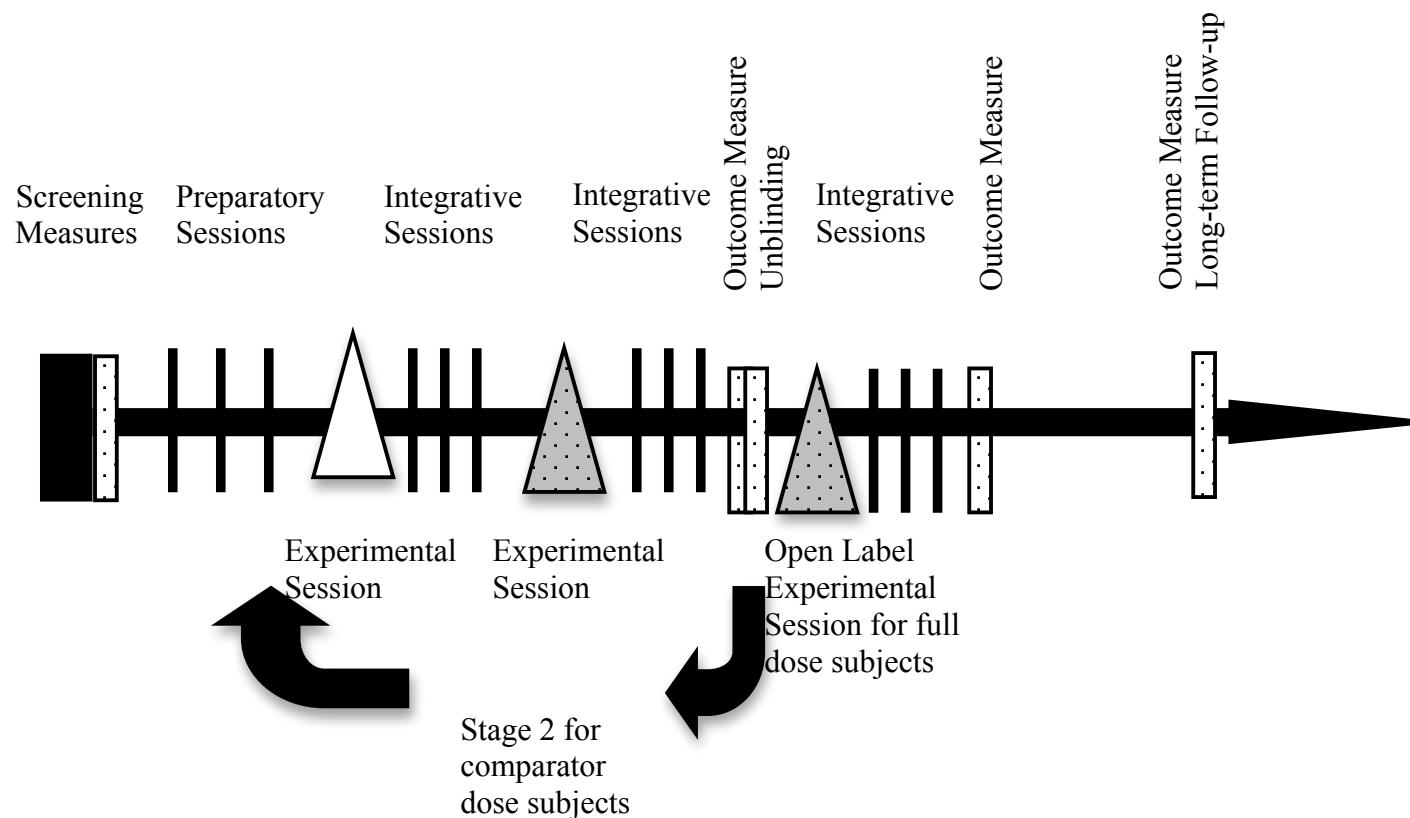
Safety: The safety of subjects will be assured during and after the experimental sessions by assessing physiological effects, psychological distress, adverse events (AEs), spontaneously reported reactions, and suicidality.

- 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.
- Subjective Units of Distress (SUD) scores and vital signs including blood pressure, heart rate and temperature will be measured during each experimental session.

- Serious Adverse Events (SAEs) will be collected through termination.
- All AEs and spontaneously reported reactions will be collected on the day of drug administration and for seven days after each experimental session.
- AEs requiring medical attention will be collected from the first experimental session through the subject's last two-month follow-up.
- AEs related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any AE leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.
- Changes in pre-existing tinnitus and/or chronic pain symptoms will be collected using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.
- Changes in memory, attention, speed of information processing and problem solving will be measured with RBANS and PASAT at the primary endpoint and two months after the final Stage 1 or Stage 2 experimental session.

Statistical Analysis: This is a pilot study intended to collect estimates of effect size of full dose MDMA (125 mg) versus placebo comparator dose. The study is underpowered for detection of differences of a small or moderate effect size, but it may detect differences if the effect size is large. 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 conditions for all available data from outcome measures. Effect sizes will be estimated for all outcome measures using Cohen's techniques. RBANS and PASAT scores at baseline and primary endpoint will be compared across conditions using difference scores and independent-sample t-tests, with p value set at 0.05. Descriptive statistics will be computed for each adherence scale within a specific given session. The sponsor will explore the factors and structure of the measures of adherence to assist in further development of adherence and competence measures. If sufficient data is available, the sponsor will correlate the mean adherence ratings for adherence scale and session type with Global CAPS scores to investigate the effects of adherence to the treatment manual on reduction in PTSD symptoms.

Figure 1. Study Structure Overview



PROTOCOL MP-4
IND #63,384

Original Protocol: March 17, 2009
Amendment 1 Version 1: October 27, 2010
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Amendment 2 Version 2: June 02, 2014
Amendment 2 Version 3: June 20, 2014

**A Randomized, Double-Blind, Controlled Phase 2 Pilot Study of Manualized
3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12
Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada**

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1.0 List of Abbreviations

AE(s)	Adverse Event(s)
AED	Automated External Defibrillator
A:G	Abumin : Globulin ratio
ALT/SGPT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory II
BP	Blood Pressure
BT	Body Temperature
BUN	Blood Urea Nitrogen
C	Celsius
CAPS	Clinician Administered PTSD Scale
CI	Clinical Investigator(s) (e.g. therapists, Sub-Investigator(s))
CPK	Creatine phosphokinase
CPT	Cognitive Processing Therapy
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	Dissociation 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
HIPA	Health Information Protection Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IR	Independent Rater
IRB	Institutional Review Board
ISF	Clinical 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
NEO-PI	Neuroticism Extroversion Openness Personality Inventory
OT	Oxytocin
PASAT	Paced Auditory Serial Addition Test
PDS	PTSD Diagnostic Scale
PI	Principal Investigator
PRN	As Needed
PSQI	Pittsburgh Sleep Quality Index
PTSD	Posttraumatic Stress Disorder
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTGI	Posttraumatic Growth Inventory
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
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-RV	Structured Clinical Interview for Diagnoses Research Version
SERT	Serotonin Transporter
SL	Sublingual
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

2.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with chronic treatment-resistant posttraumatic stress disorder (PTSD). This study, seeking to test MDMA-assisted psychotherapy in Canadian residents with chronic treatment-resistant PTSD, is part of an international series of Phase 2 clinical trials. Ongoing and planned Phase 2 studies are laying the groundwork for a possible End-of-Phase 2 meeting with FDA and Phase 3 multi-site studies.

MAPS has published results indicating sustained improvements in PTSD severity after MDMA-assisted psychotherapy [1-3]. MAPS is currently conducting a U.S.-based Phase 2 trial treating U.S. military veterans, firefighters, and police officers with service-related, chronic, treatment-resistant PTSD, a U.S. Phase 2 pilot study in 12 subjects in Boulder, Colorado, and an Israeli Phase 2 pilot study in 10 subjects. Taken together, these pilot studies will help to gather preliminary data about the safety and efficacy of MDMA-assisted psychotherapy that will inform the design of possible Phase 3 multi-site studies.

This Canadian pilot study is a randomized, double-blind, placebo-controlled evaluation of MDMA-assisted psychotherapy in 12 patients with chronic, treatment-resistant PTSD. PTSD must be of at least 6 months duration without remission from prior treatment with either pharmacotherapy or psychotherapy of adequate dose/duration or where treatment was discontinued due to lack of tolerability. This study is designed to obtain estimates of effect size for safety and efficacy. The data will be combined with ongoing Phase 2 dose response studies in a meta-analysis.

This pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, seven of 12 people will receive a dose of MDMA expected to be fully therapeutic (full dose) and five of 12 will receive a comparator dose of 0 mg (inactive placebo) during the blinded part of the study, referred to as Stage 1. PTSD and associated symptoms will be assessed at baseline and one month after the second double-blind MDMA-assisted (experimental) psychotherapy session. Cognitive function will also be assessed at baseline and again one month after the second experimental session. Study subjects will receive psychotherapy before and after each experimental session.

Unblinding will take place after the primary endpoint assessments. Full dose subjects will continue in Stage 1 and receive a third MDMA-assisted (experimental) psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over and take part in a second study segment, referred to as Stage 2, with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Stage 2 follows similar procedures and visit schedule as Stage 1 using varied active doses of MDMA, in which each initial dose

may be followed by a supplemental dose that will be half of the initial dose. In Stage 2, subjects will receive an initial dose of 100 mg MDMA during the first experimental session. The co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg MDMA in the second and third experimental sessions.

3.0 Background

3.1 Posttraumatic Stress Disorder

PTSD is a debilitating psychiatric disorder arising after a traumatic life event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. A complex biopsychosocial condition, PTSD is characterized by a combination of three types of symptoms:

1. Hyperarousal symptoms such as hypervigilance, anxiety, and sleep disturbance.
2. Intrusive re-experiencing of traumatic experiences, such as intrusive memories, nightmares, or flashbacks.
3. Avoidance symptoms, including emotional numbing and withdrawal [4, 5].

The DSM-IV criteria for PTSD include:

- Exposure to a significant traumatic event accompanied by an intense, acute emotional response.
- Persistent re-experiencing of the event or aspects of the experience.
- Persistent avoidance of stimuli associated with the event and/or withdrawal from some aspects of life.
- Persistent symptoms of increased arousal.
- 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 [11-14]. According to some estimates, PTSD appears to be less prevalent in the general population of Europe at 1.9% [13]. In U.S. military personnel returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [15]. It is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [16]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [14, 17, 18].

Although presently we are not aware of any national surveys of lifetime PTSD prevalence in Canada, it is likely that the percentage of Canadians experiencing PTSD is similar to the 8% to 11% listed in samples from the United States and Europe. Likewise, a large prospective, longitudinal epidemiological study of adolescents and young adults in Germany showed a lifetime prevalence of PTSD, including sub-threshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased

to 10.3% [19]. A survey of 3062 women in Ontario reported a 10.7% lifetime prevalence rate [20]. A study of Canadian peacekeepers reported higher rates of prevalence, with peacekeepers with single deployment diagnosed with PTSD at a rate of 10.9% and a 14.8% rate in peacekeepers that were deployed more than once [21]. These findings suggest that Canadians have PTSD at rates comparable to the US and Europe and that as expected, certain populations will experience higher rates of PTSD.

PTSD is clearly a serious public health problem and contributes substantially to healthcare costs [5, 8, 9]. PTSD is typically a chronic illness [6, 22] associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [7-10, 23]. People suffering from PTSD face challenges in relationships and work productivity [24]. Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [25]. Two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, which are known to affect the serotonergic components of PTSD, are currently marketed as PTSD medications in the U.S. [26, 27]. SSRIs must be used every day in order to be effective for PTSD symptoms [28]. However, SSRIs are associated with a high rate of discontinuation due to lack of tolerability caused by treatment-emergent side effects that may be under-reported [29, 30].

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 [31-33]. 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 [34]. 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 Clinician Administered PTSD Scale (CAPS) scores, an outcome which was considered highly efficacious [35]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [26] and another randomized, double-blind study found no difference between sertraline and placebo in the treatment of PTSD [36]. 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 [37-39]. 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 [40, 41], although some patients may need more than one type of treatment to reduce or resolve those symptoms [28]. A recent meta-analysis concluded that all “bona fide” psychotherapies, including those listed above, are similarly effective with PTSD [42]. 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 [43] for a review). Examples of this are virtual reality-assisted exposure therapy [44-47] and D-cycloserine-assisted psychotherapy [48]. MDMA-assisted psychotherapy is another such approach.

3.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative. Chemists at the Merck pharmaceutical company first synthesized it in 1912 [49, 50], though its clinical effects were not subject to formal investigation until the 1980s. MDMA is a potent monoamine releaser that has its greatest effects on serotonin, followed by norepinephrine and dopamine [51-56].

MDMA acutely decreases activity in the left amygdala [57], a brain region involved in interpretation of negative cues, and attenuates amygdalar response to angry faces [58]. This action of MDMA is compatible with its reported reduction in fear of emotional injury or defensiveness [59]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [58]. A recent study in healthy volunteers found correlations between oxytocin (OT) levels, amygdalar volume, and extraverted personality [60].

OT is a neuropeptide associated with pair bonding and social affiliation in mammals that also attenuates amygdalar response to anxiogenic stimuli [61, 62]. OT administration is associated with increased interpersonal trust and changes in social perception, including attenuated reactivity to threatening faces [63-66]. MDMA elevates OT in peripheral blood [67-69], which is an imperfect but somewhat reliable indicator of elevated OT in the brain [62]. Findings of an association between elevated OT and detectable MDMA in peripheral blood were first reported in a naturalistic study of London nightclub attendees with and without detectable serum MDMA levels [67]. Dumont and colleagues reproduced these results in humans and found that MDMA significantly elevated peripheral plasma OT levels in a placebo-controlled study in healthy volunteers [68], in addition to a positive association between elevated levels of OT and prosocial feelings. Hysek and colleagues replicated these results and reported that administering a serotonin reuptake inhibitor, but not a norepinephrine uptake inhibitor nor several adrenergic antagonists, attenuated the effects of MDMA on OT levels, suggesting a serotonergic mechanism in producing elevated OT [69]. The effects of MDMA on OT may influence empathy or compassion for self and others, decrease defensiveness, and strengthen therapeutic alliance. The multi-level effects of MDMA on monoaminergic signaling and OT, combined with a therapeutic setting, are more likely to provide the opportunity for a corrective emotional experience than OT alone, and could be useful in the treatment of PTSD.

3.3 Previous Clinical Experience with MDMA

Classification as a Schedule I drug in the United States has hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and efficacy of MDMA-assisted psychotherapy has become more feasible due to an open IND with

the FDA [70]. The first double-blind, placebo-controlled U.S. Phase 1 study sanctioned by the FDA was conducted at Harbor-UCLA Medical Center in 1994, with findings that suggested MDMA may cause a statistically significant increase in body temperature, heart rate, and blood pressure in some healthy volunteers [71]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [68, 71-76]. The elevation in body temperature noted in healthy volunteers was not clinically significant in sponsor-supported studies at normal ambient temperatures [1, 77]. As of May 2013, MDMA has been administered to more than 845 research subjects, in both Phase 1 and Phase 2 studies, and the sponsor has not been informed of or seen published reports of any unexpected MDMA-related Serious Adverse Events (SAEs) in research studies [1, 51, 54, 58, 59, 68, 69, 71, 72, 74, 76-108].

The potentially therapeutic effects of MDMA were initially investigated in a dose response pilot study funded by MAPS in Spain, in six female survivors of sexual assault with treatment-resistant PTSD [78, 109]. In this study, doses ranging from 50 mg to 75 mg demonstrated mild signs of improvement without any adverse events (AEs) or signs of deteriorating mental health [109].

MAPS sponsored the first U.S. Phase 2 randomized, placebo-controlled study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD, designated as MP-1. MP-1 demonstrated promising results in a sample of 20 subjects [77]. 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 at two-month follow-up. Data from this randomized, placebo-controlled pilot study suggests that MDMA is associated with significantly greater improvement in PTSD than placebo (N=20) [77]. Two months after treatment with MDMA-assisted psychotherapy, 83.3% (8 of 12) of the subjects no longer had a PTSD diagnosis and exhibited a 68% drop in CAPS global severity scores. Twenty five percent (two of eight) of the subjects in the placebo and psychotherapy group no longer had a PTSD diagnosis and exhibited a 26% drop in CAPS global severity scores. Seven of the eight subjects receiving placebo went through the treatment program again to receive full dose MDMA. The crossover subjects experienced a 48% drop in CAPS scores and none of these subjects qualified for a PTSD diagnosis at the end of the study, establishing that subjects receiving placebo were not more resistant to treatment. Evaluation of subjects on an average of 45.4 months after receiving MDMA-assisted psychotherapy indicates that the therapeutic benefits have been sustained over time on average, although two subjects experienced a relapse in PTSD symptoms [3]. PTSD symptom severity in subjects who completed the CAPS at long-term follow-up (mean CAPS scores 23.7 ± 22.8 , N=16) were statistically equivalent on average to the end of the treatment program (mean CAPS scores 24.6 ± 18.6 , N=16) [3].

The sponsor also supported a randomized, double-blind pilot study in 12 subjects with chronic, treatment-resistant PTSD in Switzerland with three experimental sessions, designated as MP-2. The study results suggested a trend toward significant improvement

in subjects receiving full dose MDMA, when compared to a 25 mg active placebo MDMA at two-month follow-up [1]. The improvement continued to increase during the 12-month follow-up [1].

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).

Overall, the results of these studies suggest that MDMA-assisted psychotherapy may be safe and effective in these subjects regardless of trauma etiology.

3.4 MDMA-assisted Psychotherapy for PTSD

MDMA-assisted psychotherapy is an innovative mode of treatment that combines therapeutic techniques with the administration of MDMA, a pharmacological adjunct that may enhance or amplify certain aspects of therapy. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to therapy. 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 [110-113]. 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 [110, 111, 114, 115] before it was placed in Schedule I in 1985, as a result of extensive non-medical use [59, 113, 116]. Placement in Schedule I prohibited it for use, except in a federally approved research setting in the U.S.

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 have found a small percentage of people exhibit problematic use of Ecstasy (material represented as containing MDMA) [117, 118]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [119]. Hence, MDMA may have moderate abuse potential. See the Investigator's Brochure (IB) for a more detailed explanation.

Many psychotherapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in psychotherapy with an appropriate level of emotional engagement [5]. To be effective, exposure must be accompanied by a degree of emotional engagement or “fear activation” while avoiding dissociation or overwhelming emotion [120]. This has been referred to as working within the “optimal arousal zone” or “window of tolerance” [121-123]. When given in an appropriate setting, MDMA produces increased positive mood, facilitates recall and imagination, changes in emotion perception, and social affiliation [58, 68, 69, 103, 124]. These effects are thought to permit revisiting of trauma-associated memories, thoughts, and feelings while maintaining the window of tolerance.

In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [59]. MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA as a pharmacological adjunct. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients, as it appears to stimulate spontaneous engagement in elements of conventional therapies, such as exposure therapy, psychodynamic therapy, and internal family systems therapy in the therapeutic context. 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. The biologic and therapeutic approaches are intended to overlap and reinforce each other.

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 [77, 109, 111, 113]. 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 [110]. 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 perspective and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to serve as an innovative treatment for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are outweighed by the possibility that this treatment may offer significant

benefits. 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.

3.5 Purpose

This Phase 2 pilot study is a randomized, double-blind, placebo controlled study in 12 subjects that will estimate the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 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, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over to Stage 2 with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

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 time 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.

Two therapy teams will conduct psychotherapy visits according the treatment manual provided. One team will consist of the Qualified Investigator and a co-therapist, and the second team will consist of a co-therapist and a Sub-investigator who have been delegated the authority to conduct therapy by the Qualified Investigator. All study procedures, including administration of the Investigational Product, will be done by the Investigator or designated qualified study personnel according to the Site Responsibility Log.

4.0 Ethics

The trial will not be initiated until appropriate Health Canada and Institutional Review Board (IRB) approval of the protocol and the informed consent document has been obtained. All documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. The protocol will also be submitted to FDA under U.S. IND #63,384.

This trial will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines, and applicable Standard Operating Procedures (SOPs). The trial will be conducted under a protocol reviewed and approved by an IRB. The trial will be conducted by scientifically and medically qualified persons. The benefits of the study will be considered in proportion to the risks. The rights and welfare of the subjects will be respected. The physicians conducting the trial do not find the hazards to outweigh the potential benefits. Each subject will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

5.0 Informed Consent

The Investigator is responsible for overseeing informed consent is obtained in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. The informed consent discussion must be conducted by a person who is qualified according to regulations. Written information about the trial will be provided in an understandable Informed Consent Form (ICF). Written consent must be given by the subject. The ICF document must be explained and the subjects' questions must be answered. 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, and that it is an inactive placebo. 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 active 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.

In addition to the explanation of study visits, the ICF 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 Investigator 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

records. 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 Health Information Protection Act (HIPA), the Investigator will have access to the subject's study related medical records and data will be used. If a subject revokes consent and HIPA, the Investigator will have access to the subject's medical records prior to the date and time of revocation but the data will not be used.

6.0 Study Objectives

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

6.1 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.

6.2 Secondary Objectives

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

- Assess changes in self-reported PTSD symptoms 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 (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) 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.
- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) 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, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, changes in personality via NEO-PI 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, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI 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, PTGI, NEO-PI, and DES-II.
- Assess the ability of the therapists 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.

6.3 Safety Objectives

The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

- Vital signs (blood pressure, heart rate, and temperature) and Subjective Units of Distress (SUD) will be measured during each experimental session. Comparisons will be made for SUD scores and vital signs between each condition.
- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session.

Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.

- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by condition, and end of Stage 1/end of Stage 2 for maximal exposure.
- 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.

7.0 General Investigational Plan

7.1 Recruitment and Subject Population

Subjects may be men or women aged 21 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 will also not be excluded for having more than one traumatic event. Subjects must have a CAPS score equal to or greater than 60 and 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. Seven of 12 subjects will be randomly assigned to receive the full dose and five subjects will be randomly assigned to receive the comparator dose.

Study subjects will be Canadian residents recruited by letters of referral sent to psychiatrists and psychotherapists, written advertisements, announcements placed on appropriate Internet sites and the sponsor site, and through word of mouth. Site staff will interview prospective subjects by telephone to learn if they meet basic eligibility criteria. If the prospective subject is interested in taking part in the study, the Study Coordinator will provide the prospective subject with consent materials for review and consideration.

7.2 Enrollment Criteria

7.2.1 Inclusion Criteria

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

1. Meet DSM-IV criteria for current PTSD, with a CAPS score of 60 or higher, indicating moderate to severe PTSD symptoms;
2. Have chronic PTSD, defined as PTSD persisting for longer than 6 months; subjects may have experienced one or more traumatic event;
3. Have treatment-resistant PTSD, who were unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, 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. Are at least 21 years old;
5. Are willing to commit to medication dosing, experimental sessions, follow-up session and completion of evaluation instruments;
6. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. 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 ten 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;
7. 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 Investigator or Sub-Investigator to communicate directly with their therapist. Subjects 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. 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;
9. Agree to take nothing by mouth except alcohol-free liquids after midnight the evening before the experimental session. Subjects must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24

hours of each experimental session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each experimental session;

10. Are willing to remain overnight at the clinic after each experimental session until the integrative session occurring the next morning. An attendant with previous training in managing psychological distress will be present to assist with personal needs if requested and offer dinner and breakfast;
11. Are willing to locate an individual to drive them home the morning after the experimental sessions, after the integrative session. If a subject is unable to locate someone to transport them home, the therapists will assist the subject in obtaining transport from the clinic to the subject's home or any other location where he or she is staying temporarily;
12. Are willing to be contacted via telephone on a daily basis by one of the therapists for a week after each experimental session;
13. Are willing to provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by the therapists in the event of a subject becoming suicidal;
14. Agree to inform the therapists within 48 hours of any planned medical interventions;
15. Have a negative pregnancy test and must agree to use an effective form of birth control, if the participant is a female of childbearing potential;
16. Are literate and proficient in reading documents written in English and speaking English;
17. Agree to have all clinic visit sessions recorded to audio and video;
18. Agree not to participate in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period.

7.2.2 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. Have dissociative identity disorder or an eating disorder with active purging;
4. Have evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, cardiac, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder, or any other medical disorder judged by the Investigator or Sub-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 of values of 140/90 or higher assessed on three separate occasions, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia;

6. Weigh less than 48 kg;
7. Have used “Ecstasy” (illicit drug preparations purported to contain MDMA) more than five times in the last 10 years or at least once within six months of enrollment;
8. Would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, as determined through psychiatric interview, responses to C-SSRS and through clinical judgment of the Investigator or Sub-Investigator;
9. Require ongoing concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs;
10. Meet DSM-IV criteria for active substance abuse or dependence for any substance other than caffeine or nicotine in the past 6 months;
11. Are not able to give adequate informed consent;
12. Have any current problem, which in the opinion of the Investigator, Sub-Investigator, or Medical Monitor, might interfere with participation in the study.

7.3 Planned Duration of Study and Visit Windows

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 complete Stage 2: 18 months

Screening may take up to two months, with the baseline CAPS being conducted 4 to 8 weeks before the first experimental session, in order to allow for appropriate medication washout of at least 5 half-lives of pre-study psychiatric medications and active metabolites, and one additional week for stabilization. For example, the maximum washout would be 7 weeks for subjects tapering off of fluoxetine plus one week for stabilization. Tapering off high doses of benzodiazepines may take a comparable period of time. Scheduling of preparatory sessions must be between screening and the first experimental session at intervals that suite the scheduling needs of participants and the research team, with the first experimental session taking place 3-5 weeks after enrollment, and at most 5 weeks after the baseline CAPS. The maximum window from the start of screening to the first experimental session is 13 weeks. The optimal timing for Stage 2 is within one month after the primary endpoint visit in Stage 1, with a maximum allowable window of five months. Any delay between visits would result in a corresponding extension of study duration.

8.0 Drug Description and Dosage

Subjects assigned to the full dose condition will receive three experimental sessions with an initial dose of 125 mg possibly followed 1.5 to 2.5 hours later by an optional supplemental dose of 62.5 mg MDMA. Subjects in the comparator dose condition will be assigned to receive two experimental sessions with an initial dose of 0 mg MDMA

possibly followed 1.5 to 2.5 hours later by an optional supplemental dose of 0 mg MDMA. Seven of 12 subjects, or 58%, will be assigned to the full dose condition, and five of 12, or 42%, will be assigned to the comparator dose condition.

Subjects in the comparator dose condition during Stage 1 will have the opportunity to cross over to Stage 2. Stage 2 will be used to explore the optimal therapeutic dose using a clinical titration dosing strategy using varied active doses of MDMA. In Stage 2 subjects will receive an initial dose of 100 mg followed 1.5 to 2.5 hours later by an optional supplemental dose of 50 mg MDMA during the first experimental session. In the second and third session they will receive an initial dose of 100 mg or 125 mg MDMA followed 1.5 to 2.5 hours later by an optional supplemental dose of 50 mg or 62.5mg as appropriate to the initial dose of MDMA. The decision to titrate the dose in the second and third session will be based on the experience of the first session, if 100mg MDMA does not seem to be the optimal therapeutic dose based on the first experimental session in Stage 2, the dosage may be increased by an increment of 25mg in order to achieve the optimal therapeutic dose. The supplemental doses for each experimental session will be half of the initial dose, respectively.

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the full dose condition are identical to those in use in other sponsor-supported studies of MDMA-assisted psychotherapy. Previous researchers have also used doses within this range [71, 72, 74, 75, 124, 125]. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [74, 75, 91, 126-128]. Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [59, 111, 113]. The initial full dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions.

The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop MDMA-assisted psychotherapy as a treatment for PTSD and in Stage 2 to develop a dose-response curve for the treatment. The Stage 1 comparator dose of 0 mg MDMA is not expected to produce the therapeutic or physiological effects of MDMA. The goal of this study is to estimate the effect size of comparator and full dose MDMA for safety and efficacy. The placebo dose will provide clear adverse event, neurocognitive and efficacy data.

Table 1. Stage 1 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose
1 and 2	Comparator Dose	0 mg	0 mg	0 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

Table 2. Stage 2 Drug Doses

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

8.1 Drug Compounding, Doses, and Labeling

The investigational product (IP) for the study is MDMA. Bulk IP will be received at the pharmacy via a secure delivery system in accordance with all local regulations. A receipt will be kept on file at the pharmacy and at the site. Seven strengths of IP will be created: 125 mg, 100 mg, 62.5 mg, 50 mg, 25 mg, 12.5 mg and 0 mg (placebo only). Each of these batches will be created with the bulk MDMA and varied amounts of lactose during the compounding process. A “packing stat” will be created by filling 10 capsules with lactose to calibrate the amount of compounded IP per capsule. Once encapsulated, the total number of capsules will be recorded on the drug accountability log.

The encapsulation will be performed by a pharmacist who has the appropriate skills. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all capsules have similar weights. The placebo capsule will consist of lactose only. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent therapists and subjects from distinguishing contents of full dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging.

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled “inner envelopes” within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to

the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

Figure 1. Examples of Drug Labels

Holding Box Labels

Holding Box Label
MAPS Study# MP-4 Investigational Product: MDMA Dose: XXmg Lot #: XXX Restricted drug for clinical trial use by Qualified investigator only

Stage 1 Primary Container Labels

Blinded

Primary Container MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 1 Blinded Experimental Session # <u> </u> Container # XXX Lot # XXX Expiry date: XXX Store at 22°C Subject # <u> </u> Restricted drug for clinical trial use by Qualified investigator only

Open Label Session 3

Primary Container MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 1 Open Label Experimental Session # <u>3</u> Container # XXX 125mg & 62.5mg MDMA Lot # XXX Expiry date: XXX Store at 22°C Subject # <u> </u> Restricted drug for clinical trial use by Qualified investigator only
--

Stage 1 Inner Envelope Labels

Blinded

Inner Envelope MAPS Study # MP-4 Stage 1 Container # XXX Initial Dose Subject # <u> </u> Restricted drug for clinical trial use by Qualified investigator only
--

Blinded

Inner Envelope MAPS Study # MP-4 Stage 1 Container # XXX Supplemental Dose Subject # <u> </u> Restricted drug for clinical trial use by Qualified investigator only

Open Label Session 3

Inner Envelope

MAPS Study # MP-4 Stage 1 Open Label Container # XXX Initial Dose 125mg MDMA Subject # <u> </u> Restricted drug for clinical trial use by Qualified investigator only
--

Open Label Session 3

Inner Envelope

MAPS Study # MP-4 Stage 1 Open Label Container # XXX Supplemental Dose 62.5mg MDMA Subject # <u> </u> Restricted drug for clinical trial use by Qualified investigator only
--

Stage 2 Primary Container Labels

Open Label	Open Label	Open Label
<p>Primary Container MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 2 Experimental Session # 1 Container # XXX 100mg & 50mg MDMA Lot #: XXX Expiry date: XXX Store at 22°C Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p>Primary Container MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 2 Experimental Session # 2 Container # XXX 100+25mg & 50+12.5mg MDMA Lot #: XXX Expiry date: XXX Store at 22°C Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p>Primary Container MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 2 Experimental Session # 3 Container # XXX 100+25mg & 50+12.5mg MDMA Lot #: XXX Expiry date: XXX Store at 22°C Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>

Stage 2 Inner Envelope Labels

Unblinded Session 1	Unblinded Session 1
<p>Inner Envelope MAPS Study # MP-4 Stage 2 Open Label Experimental Session # 1 Container # XXX Initial Dose 100mg MDMA Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p>Inner Envelope MAPS Study # MP-4 Stage 2 Open Label Experimental Session # 1 Container # XXX Supplemental Dose 50mg MDMA Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>
Unblinded Session 2 or 3	Unblinded Session 2 or 3
<p>Inner Envelope MAPS Study # MP-4 Stage 2 Open Label Experimental Session # _____ Container # XXX Initial Dose 100mg MDMA Open Label Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p>Inner Envelope MAPS Study # MP-4 Stage 2 Open Label Experimental Session # _____ Container # XXX Initial Dose increment 25mg MDMA Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>

8.2 MDMA Accountability

Forms will be provided to track drug accountability and administration throughout the study. Blinded drug accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all provincial and national regulations and forms pertaining to the use of controlled substances in Canada, and forms will be maintained by the pharmacist.

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

8.3 MDMA Storage and Handling

MDMA is a Schedule III compound in Canada and the pharmacist will store and handle it in compliance with relevant Federal and Province regulations. The pharmacist will be responsible for storing and dispensing the MDMA in accordance with all regulatory requirements. The IP will be stored at room temperature in a locked safe at the pharmacy and only the pharmacist will have access to it.

IP will only be removed for a single experimental session at a time and will be administered orally at the site by the Investigator or Sub-Investigator. All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each experimental session. Supplemental doses are provided for each experimental session but are optional to use. In addition, the clinical titration doses with corresponding supplemental dose are provided in Stage 2 session 2 and 3 and are optional to use.

The pharmacist will dispense one primary container with the appropriate container number to the Investigator or Sub-Investigator before each experimental session. If the Investigator or Sub-Investigator decides not to administer the optional supplemental dose and/or the optional clinical titration dose in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. Within 24 hours of the end of the experimental session (as soon as possible within the working hours of the pharmacy), the Investigator or Sub-Investigator will return the container and any remaining unused capsules to the Pharmacist for return to the pharmacy safe. At the end of the study, the Sponsor will be consulted to determine the course of action if there is any unused IP remaining.

9.0 Method

This Phase 2 pilot study is a randomized, double-blind, controlled study in 12 subjects comparing the effect size of comparator dose to full dose MDMA as an adjunct to manualized MDMA-assisted psychotherapy. Two therapy teams will conduct psychotherapy visits according to the treatment manual provided. The teams will consist of two therapists who will work together, with a physician on each team. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 of the study will consist of two blinded experimental sessions for all subjects and one open-label experimental session for full dose subjects, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. Each subject will be unblinded after completion of outcome measures at the primary endpoint, one month after the second experimental session in Stage 1. 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 as well as the equivalent time points in Stage 2. After unblinding, full dose subjects will have one more full dose session in Stage 1 and comparator dose subjects will have the opportunity

to cross over to open-label Stage 2, which will be used to explore the optimal therapeutic dose for cross over subjects. 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 a dose comparison of PTSD symptoms to MDMA-assisted psychotherapy.

9.1 Randomization

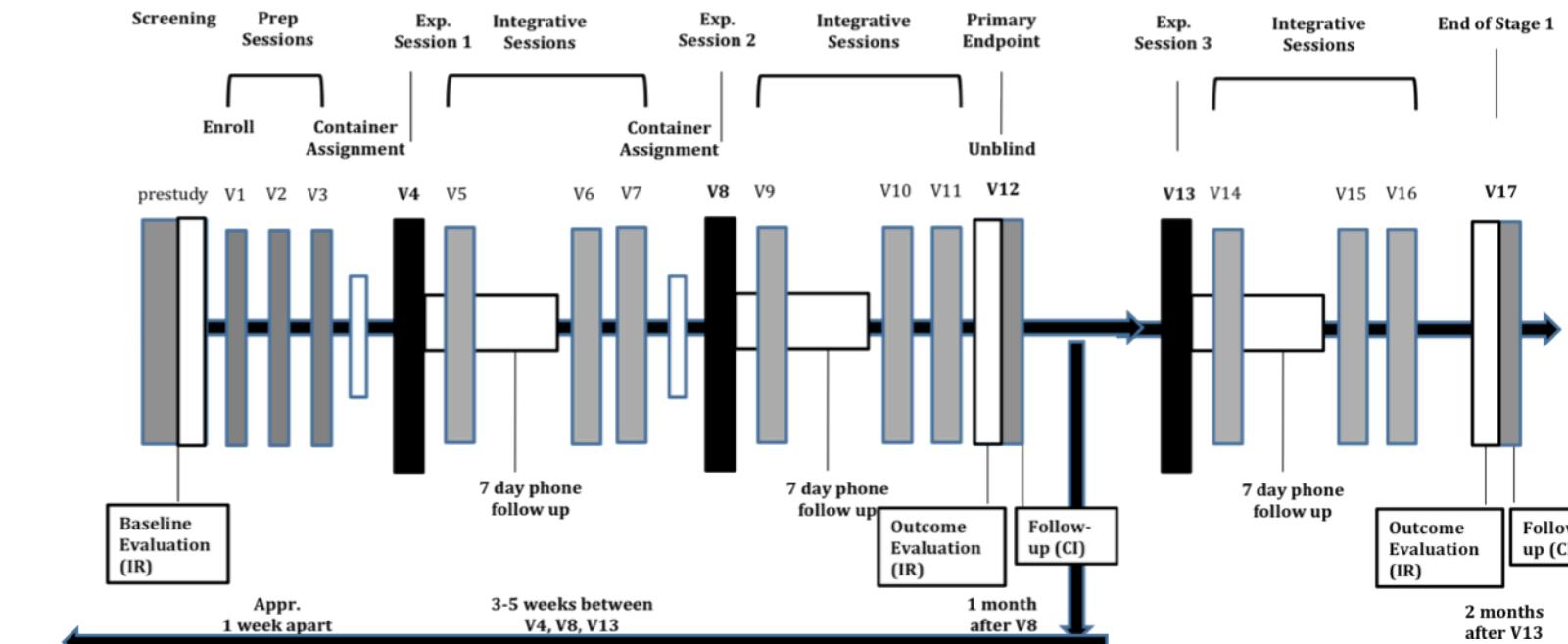
In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions. An unblinded randomization monitor will generate the randomization list prior to enrollment of subjects. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the Investigator or Sub-Investigator or designated study personnel with the randomization enrollment code corresponding to that subject's sequential subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The Investigator or Sub-Investigator or designated study personnel will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded 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.

The therapists, the IR, and all site personnel except the pharmacist will remain blind to condition assignment. If there is an adverse event or other emergency requiring knowledge of the subject's condition assignment, the blind may be broken for an individual subject by contacting the Sponsor's Randomization Monitor. In most cases it should be sufficient to inform the treating physician for the emergency that the subject had received a minimum of 0 mg MDMA and a maximum of 125mg MDMA with a supplemental dose of 62.5mg MDMA.

9.2 Subject Numbering

Prior to enrollment, subjects will be tracked with a secondary identifier number and a screening number assigned sequentially starting at "001". Subjects who meet the enrollment criteria will be enrolled in the study and assigned a 5-digit subject number. The first two digits identify the study site. The next three digits identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 04001, second 04002, etc.

Stage 1 Summary of Events



Stage 2 Summary of Events

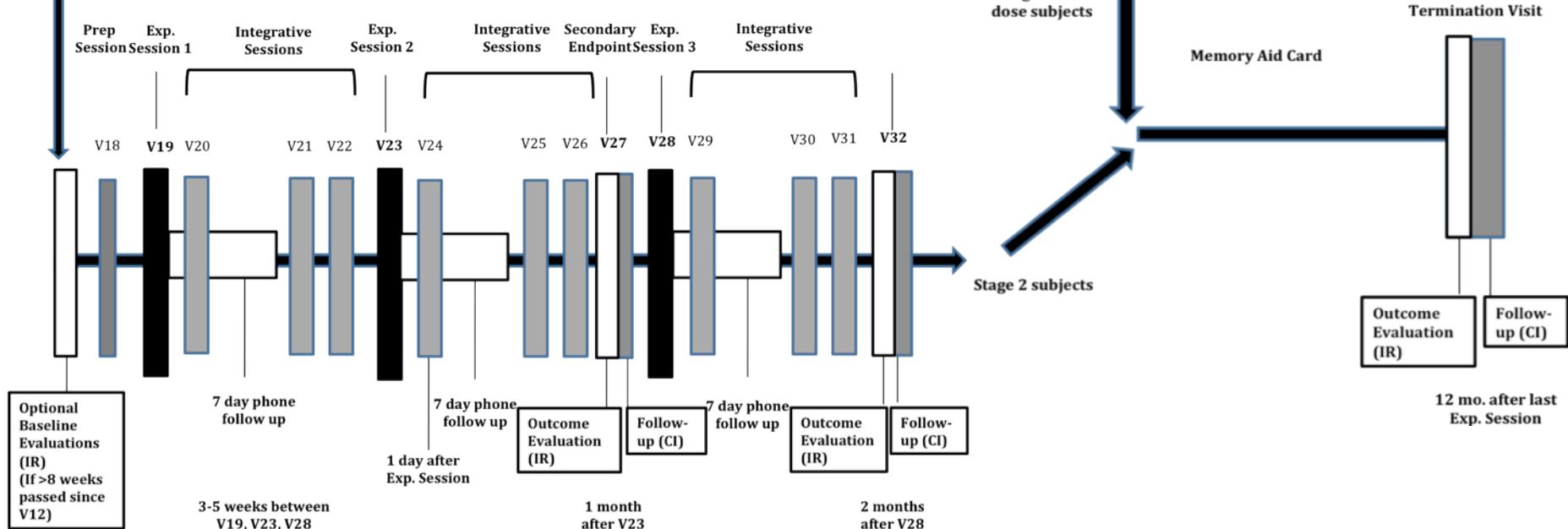


Table 3. Time & Events Stage 1

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 – see Section 7.3 for visit windows	Up to 2 months prior to V1	Between baseline and V4	within 13 weeks post CAPS	Between V4 and V8	2-5 weeks post V4	Between V8 and V12	3-5 weeks post V8	3-5 weeks post V8	Between V13 and V17	7-10 weeks post V13
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Physical Exam, ECG	✓									
Brief Neurological Exam	✓									
SCID-RV (IR)	✓									
Clinical Lab Tests with HIV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication Taper (if applicable)		✓								
Study Enrollment (if eligible)		✓ ^O								
Record to Audio/Video		✓	✓	✓	✓	✓		✓	✓	
General Wellbeing		✓	✓	✓	✓	✓	✓	✓	✓	
Drug Screen	✓		✓		✓			✓		
Pregnancy Screen (if applicable)	✓		✓		✓			✓		
Obtain Container Assignment			✓ ^B		✓ ^B					
CAPS, GAF, BDI-II, NEO-PI, PSQI, PTGI, DES-II	✓						✓ ^L			✓ ^Q
RBANS/PASAT	✓						✓			✓
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			✓ ^{F, E}		✓ ^{F, E}			✓ ^{F, E}		
Belief of Condition Assignment				✓ ^K		✓ ^K				
Overnight Stay, SOCQ			✓		✓			✓		
Integrative Therapy Session				✓ ^A		✓ ^A			✓ ^A	
7 Days Integrative 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 Experimental Sessions							✓ ^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 LTFU; I = Every face to face visit and 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 = After unblinding for full dose subjects only; O = Only on Visit 1; P = Only in subjects with pre-existing tinnitus and/or chronic pain; Q = All measures listed except for the NEO-Cl.

Table 4. Time & Events Stage 2

Study Phase	Preparatory Sessions	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 – See Section 7.3 for visit windows	Within 1 month post V12*	+/_ 1 week post V18	Between V19 and V23	2-5 weeks post V19	Between V23 and V27	3-5 weeks post V23	3-5 weeks post V23	Between V28 and V32	7-10 Weeks 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 Wellbeing	✓	✓	✓	✓	✓	✓	✓	✓		
Drug Screen		✓		✓			✓			
Pregnancy Screen (if applicable)		✓		✓			✓			
CAPS, GAF, BDI-II, NEO-PI, PSQI, PTGI, DES-II	Use V12*					✓ ^H			✓	✓
RBANS/PASAT									✓	
PDS	Use V12*		✓ ^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 Integrative 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,D}	✓ ^{J,D}	✓ ^{J,D}	✓ ^{J,D}	✓ ^J
AEs of Psychiatric Status or Withdrawal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Perception of Experimental Sessions						✓			✓	
Complete Stage 2, Go to Follow-up									✓	
RRPQ									✓	
Issue Memory Aid Card									✓	
Follow-up Questionnaire										✓
Termination Visit										✓

* If Visit 18 is more than 8 weeks after Visit 12, then subjects will need to repeat measures prior to starting Stage 2 with the exception of NEO-PI.

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 = Every face to face visit and 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; K = All measures listed except for the NEO-PI

9.3 Assessments and Measures

Screening and outcome measures were chosen to be well recognized in the literature and because of prior use in other sponsor-supported studies of MDMA-assisted psychotherapy in people with PTSD.

Eligibility for the study will be determined based on psychiatric diagnoses confirmed during screening through medical history, the Structured Clinical Interview for Diagnoses (SCID-RV) and the CAPS.

9.3.1 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 time points according to the Time and Events Table. The baseline CAPS will be administered by the IR during a face-to-face visit, with administration of the CAPS being conducted via telemedicine or in person at subsequent visits. 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. All assessments, including those at baseline, will use the CAPS assessment of symptoms over the last month. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [129, 130].

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 [131]. 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-RV diagnosis, with kappa = 0.65 [131]. Subjects will complete the PDS questionnaire at baseline, after the first and third experimental sessions, at the primary endpoint, at the end of Stage 1, and equivalent time points in Stage 2 and at the Long Term Follow-up, as specified in the Time and Events Table.

The Global Assessment of Function (GAF) is a measure of general function made through clinical observation. The GAF consists of a single score, ranging from 0 to 100, with 100 reflecting superior function and 0 reflecting serious risk of causing harm to the self or others. The IR administering the CAPS will perform the GAF assessment with the baseline GAF being administered during a face-to-face visit. Administration of the GAF at subsequent visits will be conducted in person or via telemedicine. The GAF will serve as a measure of global functioning and will be performed at the same times the CAPS is administered.

The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life [132, 133]. In this study, subjects will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions. Subjects will complete the PTGI according to the Time and Events table.

The BDI-II is a 1996 revision of the BDI, a 21-item self-report measure [134, 135], that will serve as a measure of depression according to DSM-IV criteria [136]. 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 10 minutes to complete [136]. 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 according to the Time and Events table.

The NEO-PI will serve as a measurement of personality [137, 138]. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model. Subjects will complete the NEO-PI according to the Time and Events table.

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item 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. Possible responses range from 0 to 4 on a five-point scale [139]. 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[139, 140]. Global scores correlate with other measures of alertness and self-reported sleep quality [141]. Subjects will complete the PSQI according to the Time and Events table.

The DES-II is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual's thoughts, feelings, or experiences into the stream of consciousness or memory [142, 143]. 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 10-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 [142]. 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 [143, 144]. There may be a relationship between experiencing dissociation and occurrence of chronic PTSD [143, 145]. Subjects will complete the DES-II according to the Time and Events table.

9.3.2 Safety Measures

Safety measures will be applied as described below to minimize risks associated with drug-assisted psychotherapy sessions. The therapists will be available via mobile phone or pager throughout the study to ensure subject safety.

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.

During the course of each MDMA-assisted psychotherapy session, the Subjective Units of Distress (SUD) scale will be used to assess degree of psychological distress experienced at various points during the session. Subject and therapists' beliefs concerning subject condition assignment (either full dose or comparator) will be assessed during the non-drug psychotherapy session occurring on the day after each experimental session. Neither the SUD scale nor condition assignment beliefs measures are outcome measures.

The Columbia Suicide Severity Rating Scale (C-SSRS) is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [146]. It assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS

consists of a series of questions, and can be administered during face-to-face interview or over the telephone. C-SSRS scores are sensitive to changes in suicidal ideation or behavior over time, and the measure demonstrates good convergent validity with other measures of suicidality [147]. The C-SSRS will be performed by the therapists or designated qualified study personnel at baseline, and repeated throughout the protocol to assess suicidality. See the Time and Events Table for a detailed schedule.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [148] is a relatively brief battery of assessments for cognitive function. It consists of 12 subtests that cover verbal and visual memory and attention and takes approximately 30 minutes to administer. Tasks include recall of lists, figures and stories, picture naming, semantic fluency, copying a figure, digit span and coding, and line orientation. Scores on the RBANS subtests can be used to obtain a total score and five index scores; attention, immediate memory, delayed memory, language and visuospatial/constructional scores. Factor analyses of the RBANS and samples of veterans and people with schizophrenia suggest that the RBANS possesses two factors rather than five [149, 150]. The RBANS has alternate forms, allowing repeated administration. Test performance by healthy controls were distinguishable from performance by people with probable Alzheimer's disease or the neurodegenerative condition Huntington's disease [151], and the test has high split-half reliability, with coefficients ranging from 0.80 to 0.88 [148]. Test-retest reliability is good for total RBANS scores in healthy controls and psychiatric patients [152]. The RBANS has been used in community-based and psychiatric samples [149, 153] and in a prospective investigation of the effects of chemotherapy upon cognitive function [154]. Each administration of the RBANS will use one of parallel forms of RBANS, and each participant will not complete the same form twice. This measure was employed as a means of assessing safety after two sessions of MDMA-assisted psychotherapy for PTSD [77]. See Time and Events Table for a detailed schedule.

The Paced Auditory Serial Addition Test (PASAT) is a measure of psychomotor speed, auditory information processing and computation ability [155]. The PASAT was originally designed to assess recovery after traumatic brain injury, and has been used subsequently to assess cognitive function in other populations [155, 156]. It takes approximately ten to 15 minutes to administer. The measure involves the addition of a series of digits presented at a three or two second interval, with responses made by adding each number to the prior digit. The PASAT consists of two alternate forms, permitting repeated administration. PASAT scoring includes collecting number of correct and incorrect responses, time to response (latency of response) and any failure to respond. There was a positive correlation between responses on the PASAT and a non-numerical paced measure. The measure is internally consistent (Cronbach's alpha of 0.90), and it has high test-retest reliability, with reliability ranging from 0.90 to 0.97 [156-158]. The first administration of the PASAT will use one of the two alternate forms, and the second administration will use the other. This measure was employed as a means of assessing safety after two sessions of MDMA-assisted psychotherapy for PTSD [77]. See Time and Events Table for a detailed schedule.

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 BP 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 [159-161]. 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 [160, 162-164]. 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 [160, 163, 164].

All AEs and spontaneously reported reactions will be collected, as described in Section 14.0. 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.

9.3.3 Process Measures

All sessions after enrollment may be recorded to audio and video, including introductory, integrative and experimental sessions for research and training purposes. These recordings will be used for further development of the manual of standard procedures for performing MDMA-assisted psychotherapy in people with PTSD.

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.

The SOCQ is a 100-item questionnaire based on the “Peak Experience Profile” designed by Pahnke and colleagues [165, 166]. 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.

Response to study participation and perceived degree of choice in taking part in the study will be assessed with the Reactions to Research Participation Questionnaire (RRPQ) [167]. Subjects will complete this measure during their final study visit, roughly six weeks after the last experimental session. The RRPQ is intended to assess the subject's experience as a research subject, perceived reasons for consenting to be a research subject and perceived freedom to take part in the study, and is a process measure.

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 (0 mg) 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.

Perceptions of the experimental sessions will be collected from each full dose subject during the primary endpoint visit after unblinding and from Stage 2 subjects during the secondary endpoint visit in Stage 2 before the third experimental session in Stage 1/Stage 2. Perceptions will be collected again at the end of Stage 1/Stage 2 according to the Time and Events Table. These perceptions are collected as a part of the sponsor's ongoing initiative to assess the therapeutic value of the third experimental session and information on the optimal therapeutic dose of MDMA.

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.

9.4 Visit Descriptions

9.4.1 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 and study coordinator 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. Screening may take up to two months, with the baseline CAPS being conducted no more than 5 – 8 weeks before the first experimental session, leaving room for appropriate medication washout of at least 5 half-lives of pre-study psychiatric medications and active metabolites, plus one week for stabilization. A window of up to 8 weeks is allowed if needed for medication tapering. If the CAPS is completed outside of this window for a subject, the Investigator or Sub-Investigator should consult the Sponsor CRA and Medical Monitor to determine if the baseline CAPS should be repeated. The maximum window from the start of screening to the first experimental session is 13 weeks. If, after reviewing all information, the Investigator or Sub-Investigator concludes 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. During the screening visit:

- 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. The Investigator or Sub-Investigator and qualified designated staff may all participate in conducting the informed consent.
- 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 CI for the treatment period of the study.
- d. Obtain medical and psychological history by interview.
- e. Collect information on pre-study and current medications.
- 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. Administer the C-SSRS to assess past and current suicide risk.
- h. A physician will perform a general physical examination. The examination will involve the following procedures:
 - Blood pressure.
 - Pulse.
 - Height.
 - Weight.
 - Body temperature.
 - Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and

extremities.

- Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function).
- Electrocardiogram (ECG).
- Serum electrolytes, metabolic profile, urinalysis and complete blood count
- 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.

Results of HIV serology will be kept confidential, and appropriate referral for counseling may be necessary in accordance with local law. 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 in the CRF. If, upon examination, there are questions raised about possible medical problems, the Investigator or Sub-Investigator 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 the following during a face-to -face interview:
- Structured Clinical Interview for Diagnoses Research Version (SCID-RV) to assess eligibility based on diagnoses, which includes a self-report questionnaire to focus on modules to use based on symptoms.
- Last month's CAPS to assess PTSD symptoms and eligibility, which may be recorded to video in as many instances as necessary to establish inter-rater reliability.
- GAF to assess general psychological function.
- PASAT to assess cognitive function.
- RBANS to assess cognitive function.

The subject will complete the following self-report measures:

- PTGI (in reference to time since the trauma)
- PDS to assess self-reported PTSD symptoms
- BDI-II to assess depression symptoms
- NEO-PI to assess changes in personality
- PSQI to assess changes in sleep quality
- DES-II to assess dissociation symptoms

9.4.2 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, the subject will be enrolled and issued a subject number.

During Visit 1:

- a. Complete a final review of Inclusion/exclusion criteria.
- b. Assess general wellbeing.
- c. Confirm eligibility and willingness to participate in study.
- d. Assess general wellbeing.
- e. Ensure medical history and medication history is complete. After enrollment new events will be collected as AEs and new medications will be collected as described in Section 14.0 of the protocol.
- f. Discuss medication tapering, if applicable. Upon confirmation of eligibility, the Investigator or Sub-Investigator 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 as specified in the Medication Tapering Table in Section 14.4 of the protocol, with the first experimental session scheduled to occur one week 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. Three preparatory sessions should be scheduled prior to the first experimental session. The preparatory sessions should be completed in time to ensure the experimental session occurs within 5 -8 weeks (plus any additional time needed for longer drug tapering) after the baseline CAPS. 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 may record all sessions to audio and video. Subjects may review recordings from these sessions upon request.

- b. Collect AEs and Medications as described in Section 14.0 of the protocol.
- 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. 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 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.
- f. Prior to the experimental session, the therapists will introduce the subject to the attendant that will remain with the subject during each overnight stay after each MDMA-assisted psychotherapy session. The attendant will be an individual with previous training in managing psychological distress.
- g. If a subject would like 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.
- h. The therapists or qualified study personnel 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.
- i. Assess general wellbeing at each preparatory session.
- j. 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 twenty-four hours of each experimental session.
 - Not use caffeine or nicotine for two hours before and six hours after ingesting the drug, or until therapists deem it safe to do so.

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

Experimental sessions of MDMA-assisted psychotherapy should be scheduled approximately 4 weeks apart (2-5 weeks). Procedures for MDMA-assisted psychotherapy will remain the same across all sessions. The dose of the drug and blinding procedures will vary based on the stage of the study.

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.

Pre-drug:

- a. At least 24 hours prior to the first experimental session the subject will be randomized. The Investigator or Sub-Investigator or designated study personnel 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 or Sub-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 if possible. Subjects may review 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 or qualified study personnel 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. Measurements can be done more frequently if body temperature exceeds more than 1°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 or Sub-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. This will be administered by the Investigator or Sub-Investigator.
- 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. An optional supplemental dose half the size of the initial dose may 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-assisted 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.

Table 5. Example Schedule of Procedures and Measures for Experimental Sessions

Approximate Time	Procedure or Action
9:00	Urine drug screen, pregnancy test, C-SSRS
9:45	Baseline BP, pulse, SUD
9:55	2 nd Baseline BP, pulse, BT, SUD
10:00	Drug Administration , begin recording to audio and video
10:30	BP, pulse
11:00	BP, pulse, SUD, BT
11:30	BP, pulse, May administer 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 to 90 minutes	SUD, temperature
Approximately six hours after administration	C-SSRS, General Wellbeing

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 shall remain available to subjects during the experimental session and for one week after via twenty-four-hour cellular phone for integration as needed.
- cc. If the Investigator or Sub-Investigator decides not to administer any optional supplemental or clinical titration doses, as described in Section 8.3, in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. At the end of the experimental session, the Investigator or Sub-Investigator will return the container and any remaining unused capsules to the pharmacy safe.
- dd. Spontaneously reported reactions, AEs, and Medications will be collected as described in Section 14.0 of the protocol.

Subjects will remain overnight in an appropriately furnished room at the study site. With the approval of the therapists, a companion may accompany the subject during the overnight stay. An attendant will check in periodically on the subject during the overnight stay, even if a companion is present. The attendant will monitor subject 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.

9.4.4 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 may be recorded to audio and video. Subjects may review these data 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, general wellbeing 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 session following the experimental session, 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 14.0 of the protocol.
- k. Remind the subjects that they will have daily phone contact for the next seven days.

9.4.5 A Week of Daily Contact

During daily phone contact:

- a. Therapists 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 integrative phone 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 wellbeing. Additional telephone contact can be initiated at the request of the therapists or subject.
- d. On the second and seventh day of phone 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 Section 14.0 of the protocol.

9.4.6 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. Some of these sessions may be done via telemedicine or phone calls.

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 if possible. Subjects may review these recordings 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 on the third integrative session after the first and third experimental sessions, 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 Section 14.0 of the protocol.
- 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.

9.4.7 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 3-5 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 complete the following assessments in person:
 - PASAT to assess cognitive function.
 - RBANS to assess cognitive function.
- b. The GAF to assess general psychological function, and CAPS to assess PTSD will be administered by the blinded IR in person or via telemedicine. CAPS interviews may be recorded to video in as many instances as necessary to establish inter-rater reliability.
- c. The subject will complete the following self-report measures:

- PTGI to assess post-traumatic growth (in reference to start of the study)
- PDS to assess PTSD symptoms.
- BDI-II to assess depression symptoms.
- NEO-PI to assess changes in personality.
- PSQI to assess changes in sleep quality.
- DES-II to assess dissociation symptoms.
- d. After completing all assessments and measures, the subject will meet with the therapists for approximately 30 minutes.
- e. The therapists or qualified study personnel will assess suicidality with the C-SSRS.
- f. General wellbeing will be assessed.
- g. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
- h. The blind will be broken for the subject's condition assignment. Only the IR will remain blind to condition assignment at this time.
- i. If the subject was assigned to receive the comparator dose, the therapists will discuss continuation to Stage 2. Comparator dose subjects will not complete the third experimental session and associated integrative sessions in Stage 1.
- j. Collect perceptions of experimental sessions from full dose subjects after unblinding.
- k. Collect AEs and medications as described in Section 14.0 of the protocol.
- l. 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.

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

Full dose subjects will repeat outcome measures 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 their final visit in Stage 1. 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. The IR will administer the CAPS in person or via telemedicine, the RBANS and PASAT will be administered in a face-to-face visit.
- b. Subjects will complete the PDS, BDI-II, DES-II and PSQI, PTGI (in reference to start of the study).
- c. 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.
- d. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
- e. The therapists or qualified study personnel will assess suicidality with the C-SSRS.
- f. Collect perceptions of experimental sessions.
- g. 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.

- h. 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.
- i. Collect AEs and medications as described in Section 14.0 of the protocol.

9.4.9 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, with the exception that the subject will complete a single preparatory psychotherapy session instead of three (see Section 9.4.2), and varied active doses of MDMA will be administered in an open-label context to explore the optimal therapeutic dose (e.g. without unblinding). Visits will be scheduled consecutively according to the Time and Events Table.
- c. Assessment of PTSD symptoms at the primary endpoint will serve as baseline assessments in Stage 2. If the start of Stage 2 is delayed for more than 8 weeks from the primary endpoint (Visit 12) to the first preparatory session in Stage 2 (Visit 18), the IR will re-administer the CAPS and GAF. The subjects will complete the PDS, BDI-II, PSQI, PTGI (in reference to start of the study), and the DES-II. These scores will be used as the baseline for comparison to assessment at the secondary endpoint and end of Stage 2.
- d. Experimental sessions will be conducted according to procedures described in Section 9.4.3.
 - 1. During the first experimental session, subjects will receive a 100mg initial dose of MDMA and may receive a 50mg optional supplemental dose of MDMA.
 - 2. At the beginning of the second and third experimental sessions, the therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg initial dose of MDMA. If a 100mg initial dose of MDMA is selected, an optional supplemental dose of 50 mg MDMA may be administered. If a 125mg initial dose of MDMA is selected, an optional supplemental dose of 62.5mg MDMA may be administered
 - 3. If the Investigator or Sub-Investigator decides not to administer the optional supplemental dose and/or the optional clinical titration dose in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. The Investigator or Sub-Investigator will return the container and any remaining unused capsules to the pharmacy for storage in the safe.
- e. Integrative sessions will be conducted according to procedures described in Sections 9.4.4 and 9.4.6.
- f. Phone calls will be conducted according to procedures described in Section 9.4.5.
- g. At the secondary endpoint based on procedures described in Section 9.4.7, the IR will administer the CAPS and GAF. Subjects will complete the PDS, BDI-II, PSQI, PTGI

(in reference to start of the study), and DES-II as described in the Time and Events Table.

- h. At the end of Stage 2 based on procedures described in Section 9.4.8, the IR will administer the CAPS, GAF, RBANS and PASAT. Subjects will complete the PDS, BDI-II, DES-II, PSQI, PTGI (in reference to start of the study), and NEO-PI as described in the Time and Events Table.
- i. The End of Stage 2 will be completed in the same manner as the End of Stage 1 as described in Section 9.4.8.
- j. Therapists will follow the most recent treatment manual in all matters relating to the psychotherapy sessions.

9.4.9 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. This visit may be audio and video recorded.

At the Long-term Follow-up visit:

- a. The IR will administer the CAPS and GAF via telemedicine or in person.
- b. Subjects will complete the PDS, BDI-II, NEO-PI, PSQI, PTGI (in reference to start of the study), and DES-II.
- c. 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 Section 14.0 of the protocol.
- d. The therapists or qualified study personnel will assess suicidality with the C-SSRS.
- e. Subjects will complete a questionnaire assessing positive and negative long-term effects of the study.
- f. A researcher who is a part of the study team may ask the subject questions about positive or negative effects about the study in person or on the phone.
- g. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
- h. Subjects will complete the termination visit at this time.

10.0 Removal of Subjects from Therapy or Assessment

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

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

If the subject develops any exclusion criteria, which in the opinion of the Medical Monitor, affects the safety of the subjects (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 Investigator or Sub-Investigator, 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 or after continuation to Stage 2 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.

11.0 Premature Discontinuation of the Study

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

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. Cohen's techniques will be used to estimate effect sizes between conditions for all outcome measures for Stage 1, Stage 2, and 12-month follow-up.

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 scores for the primary outcome analysis 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.

For exploratory purposes, the sponsor will examine PDS, BDI-II, GAF, PSQI, PTGI, NEO-PI, 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. Changes in outcome measures from the primary/secondary endpoint to the 2-month follow-up in Stage 1/Stage 2 will be compared for a within-subject analysis with p value set at 0.05 to see whether a third session produces further decline in symptoms.

An exploratory repeated measures analysis of variance (ANOVA) will be performed upon PDS scores at baseline, after each experimental session, at the primary endpoint, 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

may 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.

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 compare CAPS, PDS, GAF, BDI-II, PSQI, PTGI, and DES-II, scores at the final assessment prior to the 12 month follow-up to the 12-month follow-up using difference scores in an independent t-test for a within-subject analysis with p value set at 0.05.

The sponsor will compare baseline and primary endpoint RBANS and PASAT scores in full dose and comparator dose conditions using difference scores in an independent sample t-test to test for significance between groups, with p value set at 0.05. The sponsor will examine the effects of maximal exposure to MDMA on neurocognitive function using the RBANS and PASAT by performing a within-subject repeated measures ANOVA with time of administration as a within-subjects factor and with p. set at 0.05.

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.

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.

The sponsor will collect ratings of adherence to the treatment manual from specifically selected types of sessions. Descriptive statistics will be computed for each adherence scale within a specific type session. The sponsor will explore the factors and structure of

the measures of adherence to assist in further development of adherence and competence measures. If sufficient data is available, the sponsor will correlate the mean adherence ratings for adherence scale and session type with Global CAPS scores to investigate the effects of adherence to the treatment manual on reduction in PTSD symptoms. If it is found that there are specific factors within the adherence scales, then the factor will be correlated with global CAPS score.

The sponsor will compute descriptive statistics for SOCQ scores from after each MDMA-assisted psychotherapy session, and average SOCQ scores for blinded experimental sessions will be compared between conditions. The data will be explored for effects of condition on domain scores in the SOCQ.

Perception of experimental sessions will be examined 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 may be correlated with difference scores calculated from the primary/secondary endpoint CAPS data compared to end of Stage 1/Stage 2 CAPS data to assess the potential contribution of expectation and self-reported response to changes in PTSD symptoms.

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

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 study is a pilot investigation intended to estimate effect sizes of the safety and efficacy of MDMA-assisted psychotherapy in people with PTSD. Because of their exploratory nature, pilot studies are often underpowered for detecting the desired effect. Because it is a pilot study in a small sample, statistical power is difficult to assess but it is likely to be low. Analyses of MAPS' completed US study of MDMA-assisted psychotherapy in 20 people with PTSD found an effect size of 1.24 for treatment efficacy, as represented by changes in CAPS score [77]. The estimated effect size for this study may be lower as a result of employing a smaller sample size. The sponsor intends to combine effect size estimates to develop a dose response curve as a meta-analyses of CAPS scores across MAPS-sponsored pilot studies.

The sponsor used Java applications created by Lenth and posted on the website listed below to calculate estimated statistical power for this study, assuming an effect size of 1 for the impact of two sessions of MDMA-assisted psychotherapy on symptoms [168], reducing the effect size to account for the hypothesized effects of using a comparator dose. The software calculated an estimated power of 0.34, 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 0.37. Statistical power estimates were not available for secondary and exploratory measures, as they were previously not used in sponsor-supported studies.

13.0 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, the subject will not receive another experimental session unless it is approved by the Investigator and the Medical Monitor.

13.1 Medical Emergencies

Psychotherapy sessions will take place in the offices of the Investigator. Subjects may sit or lie on a couch or bed. The offices are furnished with beds that allow for two people to remain overnight. They can be heated or cooled with fans. One therapist can reach the offices within five to 10 minutes of contact if necessary. The study site will contain equipment for assessing blood pressure, pulse, and body temperature and there will be an automatic external defibrillator (AED) on site. The therapists will maintain basic life support (BLS) certification or its equivalent in Canada in cardiopulmonary resuscitation (CPR) including training in using an AED. The site is five minutes from the University of British Columbia emergency department and eight to 15 minutes away from St. Paul's Hospital emergency department. In the event of a medical emergency paramedics will be summoned and study subjects will be transported to either hospital as appropriate. This is an adequate level of emergency backup based on experience with previous Phase 2 studies in the U.S. and Switzerland during which there have been no adverse events during experimental sessions requiring emergency treatment.

The first U.S. Phase 2 trial with MDMA was conducted in an outpatient setting with a “crash cart” of emergency equipment on hand and an emergency physician and nurse in the building. The estimated transport time from this site to the nearest hospital emergency department was approximately 10 minutes with an estimated response time for an emergency medical services ambulance of approximately eight minutes. In this study,

MDMA was administered on 51 different occasions at a dose of either 125 mg by mouth or 125 mg followed in 2 to 2.5 hours by an additional 62.5 mg. Blood pressure, pulse, and temperature were closely monitored but never reached levels that required intervention nor were there any other medical problems requiring treatment during the MDMA-assisted sessions. Subsequently, a similar study was completed in Switzerland and was conducted in an outpatient psychiatry office, approximately five minutes from the nearest hospital without a crash cart or emergency personnel on site. The Swiss therapists have administered 125 mg followed by 62.5 mg MDMA on 39 occasions and administered 150 mg MDMA on four occasions without medical incident.

14.0 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. 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 until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator or Sub-Investigator and Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” CRF will be determined by the Investigator or Sub-Investigator as:

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

The relationship of the study treatment to an AE will be determined by the Investigator or Sub-Investigator based on the following definitions:

- “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.

- “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.
- “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.

14.1 Serious Adverse Events

A serious adverse event (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 or Sub-Investigator, at immediate risk of death from the event as it occurred); it does not refer to an event, which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person’s ability to conduct normal life functions).
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent permanent impairment or damage.
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events 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 serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as an on study SAE unless, in the view of the Investigator or Sub-Investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis, or abortion does not result in an SAE report unless, in the view of the Investigator or Sub-Investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

14.2 Adverse Event Collection

The Investigator or Sub-Investigator will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The Investigator or Sub-Investigator and/or qualified study personnel 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 Investigator, 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.

SAE Reporting:

MAPS Office

Telephone: 831-429-6362, ext. 104

Fax: 831-429-6370

Medical Monitor:

Michael C. Mithoefer, M.D.

Email: mmmithoefer@mac.com

Telephone: 843-849-6899 (office) 843-566-4252 (cell)

Fax number: 843-278-9188

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

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

- All SAEs will be collected through 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 or Sub-Investigator. This information may be collected by phone.

14.3 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.

14.4 Collection of Concomitant Medications and Tapering Instructions

The Investigator, Sub-Investigator, or designated study personnel 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 Investigator, Sub-Investigator or qualified study personnel 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 and active metabolites half-life).

If a subject is taking opiates for pain control they may continue them if necessary in the opinion of the Investigator or Sub-Investigator and Medical Monitor, but will be asked to taper to the lowest dose possible by the day of the experimental sessions. The dose and method of tapering should be agreed upon by the subject, the investigator or Sub-Investigator and the prescribing physician. If the subject is using opiates as needed (PRN) but not every day they should be asked to refrain from taking them the morning of the experimental session.

The therapists or designated study personnel will request information about any changes in medication just prior to each experimental session. The Investigator or Sub-Investigator 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 14.0, 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.

Table 6. Medication Tapering Table

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

The Investigator or Sub-Investigator 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 Stage 1/Stage 2 visit and the 12-month follow-up. Subjects will use this card to record changes in psychiatric medications that they will be asked about at the termination visit. Memory aids will not be collected. Subjects may return to taking psychiatric medications and discontinue birth control after the final two-month assessment if necessary.

14.5 Clinical Laboratory Assessments

The Investigator or Sub-Investigator will examine laboratory assessments gathered in screening for assessing subject eligibility. The Investigator or Sub-Investigator will use a list of normal ranges to conclude whether subjects are eligible for the protocol, and will indicate justification for admitting subjects with abnormal values, 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
 - 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
 - Blood in urine
 - Leukocyte esterase
 - Nitrite
- 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 clinical lab assessments and ECG will be performed by:

LifeLabs Medical Laboratory Services

15.0 Study Monitoring, Auditing, and Documentation

The Investigator, Sub-Investigator, therapists, and their study staff will be trained prior to the start of the study. The clinical study site will be monitored by site visits and regular contact with the Investigator and qualified study personnel by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. During each monitoring visit, source data verification will be performed by a Clinical Research Associate to ensure compliance, including accurate and complete recording of data in CRFs, source documents, and drug accountability records, while maintaining the blind during Stage 1. CRFs will be supplied by the sponsor will be completed for each subject enrolled. Monitoring and auditing procedures of the sponsor will be followed in order to comply with GCP guidelines and to ensure validity of the study data. Monitoring and auditing procedures will be supplied in a separate document.

The sponsor will review the study documentation used for planning, conduct, and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the IB, the Protocol, the CRFs, and the Subject Information and Consent Form.

During or after the clinical 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.

16.0 Risks of Participation

16.1 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 may 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.

As with any medical procedure, there are potential risks associated with the use of telemedicine. In rare cases, information transmitted may not be sufficient (e.g. poor resolution or choppy video connection) to allow for appropriate medical decision making by your therapy team or the researchers. Delays in medical evaluation and treatment could occur due to deficiencies or failures of the equipment or internet service. In very rare instances, security protocols could fail, causing a breach of privacy of personal medical information.

16.2 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 [74, 169, 170]. Women may be more sensitive to these effects [124]. 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 [171]. 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 IB.

16.2.1 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 IB.

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 Investigator or Sub-Investigator. Any subject who experiences medical complications during an experimental session will not be given another experimental session unless it is approved by the Investigator or Sub-Investigator and the Medical Monitor.

In case of need, subjects will be transferred to the emergency room at the closest hospital, as described in Section 13.1. 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 Investigator or Sub-Investigator may, at any time, make a clinical judgment to transfer the patient to the ED for closer monitoring and additional treatment.

The Investigator or Sub-Investigator 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 Investigator or Sub-Investigator 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 Investigator or Sub-Investigator, whether or not they are associated with hypertensive crisis, paramedics will be summoned to initiate the applicable protocols for further evaluation and stabilization and 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 [172, 173].

The Investigator or Sub-Investigator 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, paramedics will be summoned to initiate the applicable protocols for further evaluation and stabilization and, 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 [174].

16.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported one to three days after MDMA administration [72, 124, 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, one or both of 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 (in person or on the phone if the visit is a phone visit) 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 Investigator or Sub-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 Investigator or Sub-Investigator 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 Investigator or Sub-Investigator will carefully evaluate the subject's emotional status.

For those subjects engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the subject's outside therapists will be involved in the management of any psychiatric complications. For those subjects engaged in an ongoing psychotherapeutic relationship with the Investigator or Sub-Investigator, the management of any psychiatric complications will be undertaken by them in their capacity as therapists.

16.2.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [124] and ambient temperature does not enhance or attenuate this slight elevation in humans [75].

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 Investigator or Sub-Investigator will be consulted for further evaluation and treatment.

16.2.4 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 [175, 176], and a third reported some developmental delays in mothers reporting use of ecstasy and other drugs during pregnancy [177].

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.

16.2.5 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [178]. 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 [179]. 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.

16.3 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 Investigator or Sub-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.

16.4 Risks and Discomforts of Receiving the Comparator Dose of Study Drug

Receiving the comparator dose of 0mg MDMA may be associated with less reduction in anxiety and a smaller drop in PTSD symptoms than after full dose MDMA. The comparator is not expected to produce the therapeutic effects of MDMA. However, it is notable participants receiving placebo in the first sponsor-supported study exhibited some reduction in PTSD symptoms after undergoing two experimental sessions [77, 180]. The comparator dose of MDMA is not expected to produce most or all of the potentially therapeutic effects of the drug, such as increased positive mood, facilitated recall, changed perception of meaning, and increased feelings of closeness to others. All participants receiving the comparator may enroll in Stage 2 and receive active doses of MDMA.

17.0 Alternative Treatments and Procedures

The alternative to participating in the research study is to decide not to take part in the study. The decision not to participate in this research study will not in any way alter or compromise the care offered to individuals receiving therapy from the Investigator or Sub-Investigator or any physician involved in this research study.

The Investigator or Sub-Investigator will discuss alternatives to study participation, including other available treatments, with all potential subjects. There are a number of recognized treatments for PTSD. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatments for PTSD include anxiety management (stress inoculation training), cognitive therapy, exposure

therapy, and psychoeducation. Psychodynamic psychotherapy and Eye Movement Desensitization and Reprocessing are also used to treat PTSD.

Drugs available in Canada for treating PTSD include paroxetine, and in the US, sertraline and paroxetine are approved for use in treatment of PTSD. Sertraline has been shown to decrease the hyperarousal and avoidance symptoms, but not the re-experiencing symptoms, of PTSD. Paroxetine has been shown to have an effect on all three categories of symptoms in approximately 62% of patients. Other medications commonly used are other SSRIs, nefazodone, venlafaxine, tricyclic antidepressants, benzodiazepines, buspirone, zolpidem, and mood stabilizers.

18.0 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 secondary identifier number on the source document and five-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.

All psychotherapy sessions and the 12-month follow-up may be recorded to video and audio. In addition the CAPS assessment may also be recorded to audio and video to establish inter-rater reliability. 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. Full names and addresses will not appear in these recordings. Audio and video recordings will only be marked with the subject's subject number. Video data will be stored on a HIPA-compliant remote server with encryption and authentication in place to ensure confidentiality. Study subjects will only be able to view their own video data by logging in to a secure HIPA-compliant server. Only HIPA-certified researchers who have signed a Data Confidentiality Agreement, completed Good Clinical Practice training, and received approval from the Investigator will be permitted to access video data for research and training purposes.

Any materials mailed to subjects will be sent along with stamped return envelopes using the office address of the 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 Investigator or Sub-Investigator 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.

19.0 Costs to Subjects

There will be no costs to subjects for any study-related procedures. Only Canadian residents with Canadian health insurance will be enrolled in the study. The sponsor (MAPS) will pay for all assessments, laboratory work, or physical examinations needed to determine study eligibility. The sponsor will also cover costs of the study drug and remaining at the study site on the night after each experimental session. The sponsor will pay for all study drugs and study procedures. The sponsor will not reimburse subjects for travel, food, and lodging. Subjects will not be paid for their participation in this study.

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 Investigator or Sub-Investigator and who will continue to receive ongoing treatment that is not related to participating in the study.

20.0 Record Retention

The Investigator must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility for 25 years in accordance with Health Canada regulations. The Investigator must consult a MAPS representative before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the Investigator as to when these documents no longer need to be retained.

21.0 Publication Policy

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

Any results of medical investigations with the sponsor products and/or publications/lectures/manuscripts based thereon, shall be exchanged and discussed by the Investigator or Sub-Investigator and the sponsor clinical research representative(s) prior to submission for publication or presentation. Due regard shall be given to the sponsor's legitimate interests, e.g. manuscript authorship, obtaining optimal patient protection, coordinating and maintaining submissions to health authorities, and coordinating with other studies in

the same field.

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

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