Study Synopsis

A Phase 1/2 Open-Label Treatment Development Study of MDMA-Assisted Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads in which 1 Member has Chronic Posttraumatic Stress Disorder (PTSD)

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Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
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Study Description: This is a small pilot Phase 1/2 open-label experimental medicine study exploring Cognitive-Behavioral Conjoint Therapy (CBCT) integrated with MDMA-assisted psychotherapy for treatment of chronic Posttraumatic Stress Disorder (PTSD). This study is not intended to lead to a registration study. This study will enroll 10 dyads, consisting of a participant diagnosed with PTSD (PTSD+ participant), and a Concerned Significant Other participant (CSO participant) who does not have a current diagnosis of PTSD, but is experiencing problems associated with psychosocial circumstances related to the PTSD+ participant's diagnosis, assessed per the V-codes in the DSM-5. The primary outcome measure is the Clinician Administered PTSD Scale according to DSM-5 (CAPS-5) administered to the PTSD+ participant. Additional measures evaluate various qualities of the relationship between PTSD+ participant and CSO participant and psychological distress in the CSO participant.

Eligible and enrolled participants will undergo a 1-month course of psychotherapy as a dyad that includes CBCT integrated with MDMA-assisted psychotherapy. Treating both members of the dyad is integral to CBCT therapy, as described in Monson and Fredman's (2012) manual [1], which will be integrated with elements of the Treatment Manual for MDMA-assisted Psychotherapy in order to modify CBCT to incorporate MDMA as a catalyst for the therapeutic process [2]. The integration of these treatments will provide the researchers with a consistent psychotherapy approach and test an experimental form of drug-assisted psychotherapy. This study is designed to obtain estimates of effect size for safety and efficacy. Since this is the first time that CBCT for PTSD is being combined with MDMA-assisted psychotherapy for PTSD, the researchers are interested in gathering preliminary information about the blending of these two therapeutic approaches.

CBCT for PTSD is a three-phase, 15-session, manualized treatment described with the acronym "R.E.S.U.M.E. Living" to convey the sequential treatment phases and to signify

the recovery-focused nature of the therapy. The "R" and "E" (Rationale for treatment and Education about PTSD and relationships) capture the overall goals of Phase 1, which are to provide a rationale for treatment and to educate the couple about PTSD and associated interpersonal problems. The "S" and "U" (Satisfaction enhancement and Undermining avoidance) stand for the overall goals of Phase 2, which are to enhance relationship satisfaction and undermine avoidance that maintains PTSD and relationship issues. Content from sessions 6 and 7 of CBCT for PTSD of Phase 2 will be completed in 2 phone or videoteleconferencing sessions during the two weeks between the Experimental Sessions. The "M" and "E" (Making meaning of the trauma and End of therapy) represent the overall goals of Phase 3, which are to make meaning of the traumatic event(s) and the end of therapy (but not the end of using the skills). All of the CBCT Sessions are 75 minutes each and include within-session practice and out-of-session assignments to facilitate the couple's skill acquisition outside of session. Each therapy team will have one therapist trained and experienced in MDMA assisted psychotherapy and one therapist trained and experienced in CBCT. Whenever possible both therapists will have had training in both methods. It is believed that MDMA may hold promise to catalyze the effects of CBCT for PTSD. Given the properties of MDMA, specifically in inducing empathy and interpersonal openness, these psychopharmacological effects are especially relevant to the purported mechanisms of CBCT for PTSD.

There are several important reasons to include significant others in PTSD treatment, and to treat them as clients versus "support persons", in addition to the data supporting the efficacy of CBCT for PTSD noted above. First, four studies have been published showing that pre-treatment interpersonal functioning affects individual treatment outcomes [3-6]. These studies consistently document that poorer pre-treatment intimate relationship functioning and social support are associated with worse individual treatment outcomes for those receiving front-line individual treatments for PTSD. Second, loved ones of those with PTSD consistently document their own psychological distress, caregiver burden, and relationship distress associated with being in relation to someone with PTSD [7]. Thus, one cannot assume a psychologically healthy significant other to be participating in therapy with someone who is diagnosed with PTSD. Third, loved ones may engage in well-meaning behaviors, but in fact may exacerbate or at least maintain individual psychopathology. This phenomenon has been termed "partner accommodation" [8, 9], and has been shown to be associated with poorer outcomes for CBCT for PTSD. Fourth, in addition to interventions aimed at intrapsychic mechanisms, the communication and connection between loved ones is a target of intervention. MDMA is expected to facilitate this communication and connection, given MDMA's purported mechanisms of action. For these reasons, CBCT for PTSD was developed to be a true interpersonal treatment for PTSD, and explains the choice to administer MDMA to both members of the dyad.

This study will combine methods described in the Treatment Manual for conducting MDMA-Assisted Psychotherapy with methods from the CBCT for PTSD manual. The MDMA assisted-psychotherapy manual is not intended to define all interactions that occur in the therapy. It provides a structure within which the therapy is expected to occur and allows individual therapist teams to include therapeutic interventions based on their own training, experience, intuition, and clinical judgment, provided the interventions are compatible with the tenor of the method and appropriate to the participant's unfolding

experience. The therapists will carefully work with the both participants to establish a sense of safety, trust, and openness to create an environment supportive of healing.

Dose Selection: This study will assess the effects of psychotherapy sessions assisted by two therapeutic doses. The first experimental dose will use 75 mg of MDMA followed 1.5 to 2 hours later by an optional dose of 37.5 mg. During the second Experimental Session an initial dose of either 100 mg or 75 mg will be administered followed by an optional supplemental half-dose 1.5 to 2 hours after the initial MDMA dose. The default dose for the second session will be 100 mg (followed by an optional supplemental half-dose), however if, after discussion with the Clinical Investigators, each participant may be permitted to stay at 75 mg (followed by an optional supplemental half-dose) for the second session.

Table i: Dose Selection

Initial MDMA Dose	Optional Supplemental MDMA Dose	Cumulative (Initial + Optional) MDMA Dose
75 mg	37.5 mg	112.5 mg
100 mg	50 mg	150 mg

MDMA appears to temporarily reduce fear and increase interpersonal trust, without clouding the sensorium or inhibiting access to emotions. MDMA may catalyze therapeutic exposure by enhancing the ability to tolerate negative or threatening emotional states and allowing patients to stay emotionally engaged without being overwhelmed by the intense emotions surrounding their condition.

The active dose of MDMA to be used in this study is similar to the full dose of 125mg followed by a supplemental half dose of 62.5mg used in previous studies in the U.S., Switzerland, and Israel. Previous researchers have also used doses within this range [10-19]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [20-22]. The MDMA doses to be used in this study have been used in previous studies sponsored by MAPS.

The initial active doses are expected to produce all the commonly reported 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.

Protocol Objectives: The overall objective of this study is to explore the safety and estimate the effect size of efficacy for MDMA-assisted psychotherapy in conjunction with CBCT on PTSD symptoms in PTSD+ participants and relationship functioning in both participants.

Primary Objective: The primary objective of the study is to assess changes in PTSD symptoms from baseline as measured by CAPS in PTSD+ participants at the Primary Endpoint.

Primary Outcome Measure: Clinician-Administered PTSD scale (CAPS) administered by a blinded Independent Rater.

Secondary Outcome Measures: Posttraumatic Stress Disorder Checklist for the DSM-5 (PCL-5), Beck Depression Inventory-II (BDI-II), Pittsburgh Sleep Quality Index (PSQI), Posttraumatic Growth Inventory (PTGI), Revised Conflict Tactics Scale (CTS-2), Emotion Regulation Questionnaire (ERQ), Interpersonal Reactivity Index (IRI), Toronto Alexithymia Scale-20 (TAS-20), Quality of Relationships Inventory (QRI), Significant Others' Responses to Trauma Scale (SORTS), Miller Social Intimacy Scale (MSIS), Inventory of Psychosocial Functioning (IPF), Trauma and Attachment Beliefs Scale (TABS), Multiscale Dissociation Inventory (MDI), and Interpersonal Closeness Measure (IPC).

Safety Measures: Columbia Suicide Severity Rating Scale (C-SSRS), Subjective Units of Distress (SUD), and vital signs including blood pressure, heart rate, and body temperature, Serious Adverse Events (SAEs), Adverse Events (AEs), spontaneously reported reactions, General Wellbeing, medications and changes to psychiatric medications, and changes in pre-existing chronic pain and/or tinnitus symptoms will be collected throughout the study using a Visual Analog Scale in any members of the dyad reporting these symptoms.

Process Measures: Reaction to Research Participation Questionnaire with the (RRPQ), Long-term Follow-up Questionnaire (LTFU).

Recruitment and Participant Population: Participants may be persons aged 18 or older including a PTSD+ participant who has been diagnosed with PTSD for at least 6 months and a CSO participant (i.e., intimate or non-intimate person) who does not have a current diagnosis of PTSD but is experiencing associated psychological distress as assesed by V-codes in the DSM-5. There is no upper age limit designated in this protocol as age alone does not put participants at increased risk and is a less specific exclusion criterion when compared with direct assessment of general health. Participants with medical conditions that would have contraindications to receiving MDMA would be excluded according to the Inclusion and Exclusion criteria. Participants with a history of suicide attempts will not be excluded unless risk of suicidal behavior is present at the time of the screening assessment. All participants will be evaluated by the CI to determine if there is a current risk of suicidal behavior. Participants will be enrolled according to the Inclusion/Exclusion criteria based on the clinical judgment of the CI.

The dyad members will be referred to individually as the PTSD+ participant and the CSO participant. PTSD+ participants would not be excluded for having more than one traumatic event. PTSD+ participants must have a last month CAPS score indicating at least moderate PTSD symptoms and must meet all inclusion criteria and no exclusion criteria at Baseline. CSO participants must also meet inclusion criteria and no exclusion criteria. Both participants must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA. Dyads will be recruited through printed ads, Internet ads, referrals from other psychiatrists, psychotherapists, or physicians, and through word of mouth. Recruitment will continue until 10 dyads that

meet all inclusion criteria without meeting any exclusion criteria are enrolled. Only IRB-approved recruitment materials and advertisements will be used for the study.

Study Procedures: After giving written informed consent, prospective dyads will be screened for eligibility. At screening, each participant will sign separate informed consents, one for the PTSD+ participant and one for the CSO participant. Both must give written informed consent in order for the dyad to be enrolled. Dyads must consist of people who are in a significant ongoing relationship, including but not limited to romantic relationships. Baseline screening procedures and assessments will be conducted for both members of the dyad. Dyads in which both members meet all inclusion and no exclusion criteria will be enrolled.

Eligible and enrolled participants will undergo a 1-month course of psychotherapy as a dyad that includes CBCT for PTSD integrated with MDMA-assisted psychotherapy. The CBCT sessions, as described in Monson and Fredman's (2012) manual [1], will be integrated with elements of the Treatment Manual for MDMA-assisted Psychotherapy [2] in order to modify CBCT to incorporate MDMA as a catalyst for the therapeutic process. Sessions will be conducted by a co-therapy team and will include Preparatory Sessions, two Experimental Sessions of MDMA-plus psychotherapy and non-drug integrative psychotherapy sessions. The primary objective is to measure changes in PTSD symptoms via CAPS global severity scores in PTSD participants at Baseline and the Primary Endpoint, one month after the 15th CBCT session.

The Experimental Sessions will last 6 to 8 hours and will be scheduled 2 weeks apart, with an intervening course of non-drug therapy. The non-drug psychotherapy includes two Preparatory Sessions prior to the first Experimental Session and five integrative CBCT sessions after each Experimental Session. Integration visits will be conducted by telemedicine (video conferencing whenever possible, telephone if there are occasions when video conferencing is not technically possible) and will include both members of the dyad. The sessions will follow a combination of the MDMA-assisted psychotherapy manual and the CBCT manual, with each method modified as needed to combine the therapies.

Safety: The safety objectives of the study are to monitor and assure safety of all participants during and after the Experimental Sessions by assessing physiological effects, psychological distress, SAEs, medical events, spontaneously reported reactions, and suicidal ideation and behavior. All of the objectives below will be assessed in both participants:

- Suicidal ideation and behavior will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) according to the Time and Events Table.
- During Experimental Sessions, Subjective Units of Distress (SUD) and vital signs including blood pressure, heart rate, and temperature will be collected.
- Serious Adverse Events (SAEs) will be collected in both groups through Study Termination. All Adverse Events (AEs) will be collected on the day of drug administration through the Primary Endpoint and will be followed to resolution.

- Any spontaneously reported reactions will be collected from the day of the Experimental Session through seven days after both Experimental Sessions. Reactions that have not resolved to Baseline level of severity after seven days will be collected on the Adverse Event Report page until resolution.
- Assess General Wellbeing (clinician-rated) at all visits and phone calls for both participants.
- AEs requiring medical attention will be collected through Study Termination.
- 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 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.
- Baseline medications and changes to psychiatric medications will be collected throughout the study.
- Changes in pre-existing chronic pain and/or tinnitus symptoms will be collected throughout the study using a Visual Analog Scale in any members of the dyad reporting these symptoms.

Statistical Analysis: This pilot RCT is the first study of its kind intended to establish preliminary effect size estimates of CBCT combined with MDMA-assisted psychotherapy for PTSD. In the absence of published effect sizes for this new treatment modality, effect sizes were estimated based on prior trials of these individual treatments. In a limited number of small pilot studies, CBCT for PTSD yielded paired-treatment effect sizes of $g > 1.0$ for improvements in PTSD on the primary outcome measure and co-morbid symptoms. The two completed controlled RCTs of MDMA-assisted psychotherapy for PTSD have yielded effect sizes of $g > 1.0$ for improvements in PTSD symptoms as well. Assuming that effect size of the combined treatment may be approximately 0.8, estimated power for a within-subject analysis with a significance level of .05 based on a 2-tailed test, is 62% for a sample size of 10 participants for the primary measure, suggesting the potential for an underpowered design, but with some possibility of detecting a within-subject effect due to treatment. Statistical power estimates were not available for secondary and exploratory measures, as they were previously not used in sponsor-supported studies.

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A Phase 1/2 Open-Label Treatment Development Study of MDMA-Assisted Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads in which 1 Member has Chronic Posttraumatic Stress Disorder (PTSD)

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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 for DSM-5
CBCT	Cognitive- Behavioral Conjoint Therapy
CI	Clinical Investigator (e.g. therapists, co-investigators)
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
CTS-2	Conflict Tactics and Aggression
DBP	Diastolic Blood Pressure
DEA	Drug Enforcement Administration
DMF	Drug Master File
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - 5
ECG/EKG	Electrocardiogram
ED	Emergency Department
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
ERQ	Emotional Regulation Questionnaire
F	Fahrenheit
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IPC	Interpersonal Closeness Measure
IPF	Inventory of Psychosocial Functioning
IR	Independent Rater
IRI	Interpersonal Reactivity Index
IRB	Institutional Review Board
ISF	Investigator Site File

IV	intra-venous
LTFU	Long-term Follow-up Questionnaire
MAOI	Monoamine oxidase inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDI	Multiscale Dissociation Inventory
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
MSIS	Miller Social Intimacy Scale
PCL	Posttraumatic Symptom Checklist
PI	Principal Clinical Investigator
PRN	As needed
PSQI	Pittsburgh Sleep Quality Index
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTGI	Posttraumatic Growth Inventory
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
QRI	Quality of Relationships Inventory
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-I-RV	Structured Clinical Interview for Diagnoses Axis I Research Version
SERT	Serotonin Transporter
SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SOCQ	States of Consciousness Questionnaire
SOP(s)	Standard Operating Procedure(s)
SORTS	Significant Others' Responses to Trauma Scale
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TABS	Trauma and Belief Attachment Scale
TAS-20	Toronto Alexithymia Scale
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

1.1 List of Tables

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2.0 Introduction, Background, and Rationale

2.1 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization sponsoring clinical trials of (MDMA)-assisted psychotherapy in patients with chronic posttraumatic stress disorder (PTSD). This small pilot Phase 1/2 open-label experimental medicine study is the first study designed to explore the effectiveness of the combination of MDMA-assisted psychotherapy with evidence-based PTSD psychotherapy treatments, such as Cognitive- Behavioral Conjoint Therapy (CBCT), in treating individuals with chronic, treatment-resistant PTSD and a significant other experiencing associated psychological distress. This is exploratory and is not intended to lead to a registration study.

MAPS has published results showing clinically and statistically significant improvements in PTSD severity from 20 participants treated in their first pilot study (MP-1) in the United States (U.S.) [23]. Findings from the long-term follow-up of MP-1 participants suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [24]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) in 12 participants suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance and a similar effect size to the initial study [25]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this participant population. Ongoing Phase 2 studies, are laying the groundwork for an eventual End-of-Phase 2 meeting with FDA and possible Phase 3 multi-site research studies with MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD.

To date, there have been three case studies [26-28], three uncontrolled trials [29-31] and one randomized controlled trial [32] demonstrating the efficacy of CBCT for PTSD. Together, the results of these studies demonstrate that receiving CBCT for PTSD can result in significant and large effect size reductions in some individuals' PTSD symptoms that are on par with, or better than, existing individual evidence-based PTSD treatments.

In addition, the treatment has been shown to lead to improvements in intimate relationship functioning and significant improvements in intimate partners' mental health [33, 34]. Research also suggests that CBCT for PTSD improves parenting satisfaction and efficacy among those with children [13], and that regardless of initial levels of intimate relationship functioning, individuals with PTSD profit from the treatment [35].

This is a Phase 1/2 open-label experimental medicine study in 10 dyads including a participant who has been diagnosed with PTSD for at least 6 months and a significant other participant (i.e., intimate or non-intimate person) who does not have a current diagnosis of PTSD and significant other experiencing associated psychological distress as assessed per the V-codes in the DSM-5. The dyad members will be referred to individually as the PTSD+ participant (diagnosed with PTSD) and the CSO Participant (concerned significant other). Eligible and enrolled participants will undergo a 1-month course of psychotherapy as a dyad that includes CBCT for PTSD integrated with MDMA-assisted psychotherapy. The CBCT sessions, as described in Monson and

Fredman's (2012) manual [1] will be integrated with elements of the Treatment Manual for MDMA-assisted Psychotherapy in order to modify CBCT to incorporate MDMA as a catalyst for the therapeutic process [2]. The integration of these treatments will provide the researcher with a consistent psychotherapy approach and test an experimental form of drug-assisted psychotherapy. This study is designed to obtain estimates of effect size for safety and efficacy. This study is also intended to contribute to the development of a manualized psychotherapeutic approach to this potential treatment. Since this is the first time that CBCT is being combined with MDMA-assisted psychotherapy for PTSD, we are interested in gathering preliminary information about the blending of these two therapeutic approaches.

2.2 Background

2.2.1 PTSD

PTSD is a debilitating psychiatric disorder arising after a traumatic life event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. A complex biopsychosocial condition that also has negative effects on families, PTSD is characterized by a combination of three types of symptoms: hyperarousal (e.g. hypervigilance, anxiety and sleep disturbance), intrusive re-experiencing of traumatic experiences (e.g. intrusive memories, nightmares or flashbacks), and avoidance symptoms, (e.g. emotional numbing and withdrawal) [36, 37]. The DSM-5 criteria for PTSD include:

a. Exposure to death, threatened death, actual or threated serious injury, or actual or threatened sexual violence
b. Persistent re-experiencing of the event or aspects of the experience
c. Persistent effortful avoidance of trauma-related stimuli after the event
d. Negative alterations in cognition and mood that began or worsened after the event
e. Trauma-related alterations in arousal and reactivity that began or worsened after the traumatic event
f. Persistence of symptoms for more than one month
g. Significant symptom-related distress or functional impairment

The lifetime prevalence of PTSD in the U.S. general population is between 6% and 10% [38-42], but it is common in other countries as well [39, 43-46]. According to some estimates, PTSD appears to be less prevalent in the general population of Europe at 1.9% [47]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [48], and it is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [49]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [50-52].

PTSD is clearly a serious public health problem and contributes substantially to healthcare costs [37, 40, 41]. PTSD is typically a chronic illness [38, 53] associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [39-42, 54]. People suffering from PTSD face challenges in relationships and work productivity [55]. Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [56]. Two

selective serotonin reuptake inhibitors (SSRI), sertraline and paroxetine, which are known to affect the serotonergic components of PTSD, are currently marketed as PTSD medications in the U.S. [57, 58]. In addition, SSRIs must be used every day in order to be effective for PTSD symptoms [59], and are associated with a high rate of discontinuation due to lack of tolerability caused by treatment-emergent side effects that may be under-reported [60, 61].

A wider array of effective treatments is 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 [62-64]. 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 [46]. Forty to 60% of PTSD patients were found to be resistant to treatment in this study. In a comparison of two types of psychotherapy for women with PTSD after sexual assault in 2002, 47% of each treatment group still satisfied diagnostic criteria for PTSD based on high Clinician Administered PTSD Scale (CAPS) scores, and this was considered highly efficacious [65]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [38], and another randomized, double-blind study found no difference between sertraline and placebo in the treatment of PTSD [57]. These findings suggest that there is still a substantial need for innovative treatments for PTSD.

Another treatment approach is to develop drugs and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD [37, 66], although some patients may need more than one type of treatment to reduce or resolve those symptoms [67]. A recent meta-analysis concluded that all “bona fide” psychotherapies, including those listed above, are similarly effective for PTSD [68]. 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 [69] for a review). Examples of this are virtual reality-assisted exposure therapy [70, 71] and D-cycloserine-assisted psychotherapy [72]. MDMA-assisted psychotherapy is another such approach.

2.2.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 [73, 74]. MDMA is a monoamine releaser that has its greatest effects on serotonin, followed by norepinephrine and dopamine [75-81]. 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 [21, 22, 82, 83]. 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 [21, 82, 84, 85] before it was placed in Schedule I in 1985 as a result of extensive non-medical use [20, 22, 86]. Placement in Schedule I prohibited it for use except in a federally approved research setting.

Oxytocin is a neurohormone associated with pair bonding and social affiliation in mammals [87]. Oxytocin administration is associated with increased interpersonal trust and attenuated reactivity to threatening faces[88, 89], and some researchers have suggested a role for oxytocin in treating PTSD [90]. MDMA has been shown to elevate serum oxytocin in humans [91, 92]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [93]. The effects of MDMA on oxytocin may increase empathy or compassion for self and others and decrease defensiveness. Findings from a recent imaging study suggests that MDMA can make recall of negative memories more tolerable [94], and other studies report increased interpersonal or social focus reflected in language use and a greater readiness to see others as empathetic and caring [95-97]. These factors taken together can provide the opportunity for a corrective emotional experience [82].

In contrast to daily administrations of SSRIs, MDMA-assisted psychotherapy consists of several drug-assisted sessions interspersed with a moderate course of non-drug psychotherapy. Thus the effects of MDMA are distinct from and go well beyond those of anti-anxiety drugs such as benzodiazepines. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users found a small percentage of people exhibit problematic use of “Ecstasy” (material represented as containing MDMA) [98, 99]. Studies of regular or problematic users indicate that on average, regular use occurs no more often than once a week [100]. Hence, MDMA may have moderate abuse potential. See the Investigator’s Brochure (IB) for a more detailed explanation.

2.2.3 Previous Clinical Experience with MDMA

Classification as a Schedule I drug hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and effectiveness of MDMA-assisted psychotherapy has become more feasible due to an open IND with the FDA [101-103]. The first double-blind, placebo controlled U.S. Phase 1 study sanctioned by the FDA was conducted in 1994, with findings that suggested MDMA caused a significant increase in body temperature and heart rate in some healthy volunteers [12]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting [12]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [10-13, 91, 104, 105] [74, 87-92]. The noted elevation in body temperature was not clinically significant [23].

The potentially therapeutic effects of MDMA were initially investigated starting in 2000 in a MAPS-sponsored dose response pilot study in Spain in women survivors of sexual assault with treatment-resistant PTSD [106, 107]. Unfortunately, the study in Spain was halted in 2002 due to political pressure from the Madrid Anti-Drug Authority. Prior to its suspension, six women were enrolled and treated in this study without any adverse events (AEs) or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 mg to 75 mg [107] [94].

MAPS went on to sponsor the first U.S. Phase 2 study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD, designated as MP-1. This study employed the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded Independent Rater (IR) at Baseline, three to five days after each Experimental Session, and two months after the final Experimental Session. Data from this randomized, placebo-controlled pilot study suggests that MDMA is associated with significantly greater improvement in PTSD than placebo (N=20), with a large effect size [23]. Findings from the long-term follow-up evaluating these participants at an average of 41 months post-treatment suggests that the therapeutic benefits have been sustained over time on average, although two participants experienced a relapse in PTSD symptoms [24]. The sponsor also supported a randomized, double-blind pilot study in 12 participants with chronic, treatment-resistant PTSD in Switzerland with three Experimental Sessions. The study results suggested a trend toward significant improvement in participants receiving full dose MDMA, when compared to 25 mg active placebo MDMA at two-month follow-up, with an effect size similar to the first study. The improvement continued to increase during the 12-month follow-up [25]. 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 participants, with no drug-related Serious Adverse Events (SAEs). Participants reported benefits that were not reflected in CAPS scores, leading to termination of the study for additional training of the Israeli therapists and research team. Most recently, in the U.S., MAPS has completed treatments in a follow-up to its initial U.S. trial with a PTSD relapse study, along with a second Phase 2 trial, specifically treating U.S. military veterans, firefighters, and police officers.

As of December 2015, MDMA has been administered to more than 1185 research participants, in both Phase 1 and Phase 2 studies, without any published or reported occurrences of unexpected drug-related SAEs [11, 23, 25, 80, 93, 94, 96, 108-130].

2.2.4 MDMA-assisted Psychotherapy and CBCT for PTSD

In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [20]. MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that may enhance or amplify certain aspects of psychotherapy. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients [91, 93, 97, 108, 112, 131, 132].

Treatment goals of MDMA-assisted psychotherapy for PTSD include alleviating symptoms, interrupting and counteracting the stress-induced neurobiological abnormalities that may be associated with the condition. In fact, the biologic and psychotherapeutic approaches overlap and reinforce each other. Knowledge about the connections between the neurobiological and therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala [132], and attenuates amygdalar response to angry faces [93]. This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD [133-135]. The reduction in stress-induced activation of the amygdala may be supported and enhanced by interacting with the therapists during and after the MDMA experience.

CBCT for PTSD is a three-phase, 15-session, manualized treatment [1] described with the acronym "R.E.S.U.M.E. Living" to convey the sequential treatment phases and to signify the recovery-focused nature of the therapy. The "R" and "E" (Rationale for treatment and Education about PTSD and relationships) capture the overall goals of Phase 1, which are to provide a rationale for treatment and to educate the couple about PTSD and associated interpersonal problems. The "S" and "U" (Satisfaction enhancement and Undermining avoidance) stand for the overall goals of Phase 2, which are to enhance relationship satisfaction and undermine avoidance that maintains PTSD and relationship issues. Content from sessions 6 and 7 of CBCT for PTSD of Phase 2 will be completed in two phone or video-teleconferencing sessions during the two weeks between the Experimental Sessions. The "M" and "E" (Making meaning of the trauma and End of therapy) represent the overall goals of Phase 3, which are to make meaning of the traumatic event(s) and the end of therapy (but not the end of using the skills). All of the CBCT Sessions are 75 minutes each and include within-session practice and out-of-session assignments to facilitate the couple's skill acquisition outside of session. Each therapy team will have one therapist trained and experienced in MDMA assisted psychotherapy and one therapist trained and experienced in CBCT. Whenever possible both therapists will have had training in both methods. It is believed that MDMA holds great promise to catalyze the effects of CBCT for PTSD. Given the properties of MDMA, specifically in inducing empathy and interpersonal openness, these psychopharmacological effects are especially relevant to the purported mechanisms of CBCT for PTSD.

This study will combine methods described in the Treatment Manual for conducting MDMA-Assisted Psychotherapy with methods from the CBCT for PTSD manual. The integration of these manuals will provide the researcher with a consistent psychotherapy approach and test an investigational form of drug-assisted psychotherapy. The MDMA assisted-psychotherapy manual is not intended to define all interactions that occur in the therapy. It provides a structure within which the therapy is expected to occur and allows individual therapist teams to include therapeutic interventions based on their own training, experience, intuition, and clinical judgment, provided the interventions are compatible with the tenor of the method and appropriate to the participants' unfolding experience. The therapists will carefully work with both participants to establish a sense of safety, trust, and openness to create an environment supportive of healing.

A combined treatment of MDMA-assisted psychotherapy and CBCT 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 [21-23, 107]. 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 [82]. Participants 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 with CBCT may enable the participants to restructure their intrapsychic realities and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

MDMA-assisted psychotherapy integrated with CBCT may be able to improve psychosocial circumstances of the CSO participant as a potential secondary benefit, either indirectly through treatment of the PTSD+ participant or directly by improving the CSO participant's perception of their own psychosocial circumstances. There are several important reasons to include significant others in PTSD treatment, and to treat them as clients versus "support persons", in addition to the data supporting the efficacy of CBCT for PTSD noted above. First, four studies have been published showing that pre-treatment interpersonal functioning affects individual treatment outcomes [3-6]. These studies consistently document that poorer pre-treatment intimate relationship functioning and social support are associated with worse individual treatment outcomes for those receiving front-line individual treatments for PTSD. Second, loved ones of those with PTSD consistently document their own psychological distress, caregiver burden, and relationship distress associated with being in relation to someone with PTSD [7]. Thus, one cannot assume a psychologically healthy significant other to be participating in therapy with someone who is diagnosed with PTSD. Third, loved ones may engage in well-meaning behaviors, but in fact may exacerbate or at least maintain individual psychopathology. This phenomenon has been termed "partner accommodation" [8, 9], and has been shown to be associated with poorer outcomes for CBCT for PTSD. Fourth, in addition to interventions aimed at intrapsychic mechanisms, the communication and connection between loved ones is a target of intervention. MDMA is expected to facilitate this communication and connection, given MDMA's purported mechanisms of action. For these reasons, CBCT for PTSD was developed to be a true interpersonal treatment for PTSD, and explains the choice to administer MDMA to both members of the dyad.

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

2.3 Protocol Purpose

This is a Phase 1/2 open-label study in 10 dyads including a participant who has been diagnosed with PTSD for at least 6 months (PTSD+ participant) and a concerned significant other participant (i.e., intimate or non-intimate person) who does not have a current diagnosis of PTSD (CSO participant). Eligible and enrolled participants will undergo a 1-month course of psychotherapy as a dyad that includes CBCT for PTSD integrated with MDMA-assisted psychotherapy. The CBCT sessions will be integrated with elements of the Treatment Manual for MDMA-assisted Psychotherapy in order to modify CBCT to incorporate MDMA as a catalyst for the therapeutic process. Separately, each treatment appears to be effective. The goal of this study and the continuing research program will be to explore whether the methods in combination will prove to be effective for treatment of chronic, treatment-resistant PTSD.

Table 1. Treatment Condition

Treatment Group	1st Experimental Session Dose	2nd Experimental Session Dose
Active MDMA-assisted Psychotherapy (N=10 dyads)	75 mg MDMA + optional 37.5 mg supplement	100 mg MDMA + optional 50 mg supplement or 75 mg MDMA + optional 37.5 mg supplement

2.4 Rationale of Dose Selection

This study will assess the effects of psychotherapy sessions assisted by two therapeutic doses. The first experimental dose will use 75 mg of MDMA followed 1.5 to 2 hours later by an optional dose of 37.5 mg. During the second Experimental Session an initial dose of either 100 mg or 75 mg will be administered followed by an optional supplemental half-dose 1.5 to 2 hours after the initial MDMA dose. The default dose for the second session will be 100 mg (followed by an optional supplemental half-dose), however if, after discussion with the Clinical Investigators, each participant may be permitted to stay at 75 mg (followed by an optional supplemental half-dose) for the second session.

Table 2: Dose Selection

Initial MDMA Dose	Optional Supplemental MDMA Dose	Cumulative (Initial + Optional) MDMA Dose
75 mg	37.5 mg	112.5 mg
100 mg	50 mg	150 mg

MDMA appears to temporarily reduce fear and increase interpersonal trust, without clouding the sensorium or inhibiting access to emotions. MDMA may catalyze therapeutic exposure by enhancing the ability to tolerate negative or threatening emotional states and allowing patients to stay emotionally engaged without being overwhelmed by the intense emotions surrounding their condition.

The active dose of MDMA to be used in this study is similar to the full dose of 125mg followed by 62.5mg supplemental dose used in previous studies in the U.S., Switzerland, and Israel. Previous researchers have also used doses within this range [10-19]. Prior to the scheduling of MDMA, similar doses and regimens were used in psychotherapy [20-

22]. The MDMA doses to be used in this study have been used in previous studies sponsored by MAPS.

The initial active doses are expected to produce all the commonly reported 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.

3.0 Protocol Objectives

The overall objective of this study is to explore the safety and estimate the effect size of efficacy for MDMA-assisted psychotherapy in conjunction with CBCT on PTSD symptoms in PTSD+ participants and relationship functioning in both participants.

3.1 Primary Objective

The primary objective of the study is to assess changes in PTSD symptoms from baseline as measured by CAPS in PTSD+ participants at the Primary Endpoint.

3.2 Secondary Objectives

Secondary and exploratory objectives are to assess changes in the dyad's relationship functioning at the midpoint and Primary Endpoints, assess changes in self- and CSO participant-reported PTSD symptoms in the PTSD+ participant, and assess problems that often co-occur with PTSD, such as depression, sleep disturbances, maladaptive beliefs about self and others, and emotion regulation difficulties.

- Assess changes in PTSD symptoms from baseline as measured by the CAPS in participants with chronic PTSD at Long-term Follow-up at 3 months and 6 months.
- Assess changes in self-reported PTSD symptoms from baseline as measured with the Posttraumatic Stress Disorder Checklist for the DSM-5 (PCL-5) at Baseline, at each Integrative Session, at the Midpoint, Primary Endpoint and Long-term Follow-up at 3 months and 6 months for both the PTSD+ participant and CSO participant (based on the (PTSD+ participant).
- Assess changes in depression symptoms from baseline with the Beck Depression Inventory-II (BDI-II) at Baseline, Midpoint, the Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in self-reported sleep quality from baseline with the Pittsburgh Sleep Quality Index (PSQI) at Baseline, Midpoint, the Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in self-reported posttraumatic growth from baseline with the Posttraumatic Growth Inventory (PTGI) by the PTSD+ participant and CSO participant (based on the PTSD+ participant) at the Midpoint, the Primary Endpoint, and Long-term Follow-up at 3 months and 6 months.
- Assess changes in psychological and physical aggression from baseline with the

Revised Conflict Tactics Scale (CTS-2) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.

- Assess changes in emotional regulation from baseline with the Emotion Regulation Questionnaire (ERQ) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in compassion, empathy, and social functioning from baseline with the Interpersonal Reactivity Index (IRI) on the day after each Experimental Session, at Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in emotion recognition and alexithymia from baseline with the Toronto Alexithymia Scale-20 (TAS-20) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in relationship satisfaction from baseline with the Quality of Relationships Inventory (QRI) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in partner accommodation from baseline with the Significant Others' Responses to Trauma Scale (SORTS) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in social intimacy from baseline with the Miller Social Intimacy Scale (MSIS) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in psychosocial functioning from baseline with the Inventory of Psychosocial Functioning (IPF) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in trauma related beliefs from baseline with the Trauma and Attachment Beliefs Scale (TABS) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in dissociative symptomology from baseline with the Multiscale Dissociation Inventory (MDI) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants.
- Assess changes in interpersonal closeness from baseline with the Interpersonal Closeness Measure (IPC) during Experimental Sessions, at the Midpoint, Primary Endpoint, Long-term Follow-up at 3 months and 6 months for both participants.

3.3 Process Objectives:

The process objectives of the study are to assess reactions to research participation.

- Assess participants' reaction to research with the RRPQ at the Endpoint for both participants.
- Assess the process of participating in this study through a Long-term Follow-up Questionnaire (LTFU) at the Long-term Follow-up at 3 months and 6 months for both participants.

3.4 Safety Objectives

The safety objectives of the study are to monitor and assure safety of all participants during and after the Experimental Sessions by assessing physiological effects, psychological distress, SAEs, medical events, spontaneously reported reactions, and suicidal ideation and behavior. All of the objectives below will be assessed in both participants.

- Suicidal ideation and behavior will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) according to the Time and Events Table.
- During Experimental Sessions, Subjective Units of Distress (SUD) and vital signs including blood pressure, heart rate, and temperature will be collected.
- Serious Adverse Events (SAEs) will be collected in both groups through Study Termination. All Adverse Events (AEs) will be collected on the day of drug administration through the Primary Endpoint and will be followed to resolution.
- Any spontaneously reported reactions will be collected from the day of the Experimental Session through seven days after both Experimental Sessions. Reactions that have not resolved to the participants' Baseline level of severity after seven days will be collected on the Adverse Event Report page until resolution.
- Assess General Wellbeing (clinician-rated) at all visits and phone calls for both the participants.
- AEs requiring medical attention will be collected through Study Termination.
- 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 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.
- Baseline medications and changes to psychiatric medications will be collected throughout the study.
- Changes in pre-existing chronic pain and/or tinnitus symptoms will be collected throughout the study using a Visual Analog Scale in any members of the dyad reporting these symptoms.

4.0 Protocol Design

This is a Phase 1/2 open-label study in 10 dyads including a participant who has been diagnosed with PTSD for at least 6 months (PTSD+ participant) and a CSO participant (i.e., intimate or non-intimate person who does not have a current diagnosis of PTSD). At screening, both members of the dyad will sign separate informed consents. Both must give written informed consent in order for the dyad to be enrolled. Dyads must consist of people who are in a significant ongoing relationship, including but not limited to romantic relationships. Baseline screening procedures and assessments will be conducted for both members of the dyad. Dyads in which both members meet all inclusion and no exclusion criteria will be enrolled.

Eligible and enrolled participants will undergo a 1-month course of psychotherapy as a dyad that includes CBCT for PTSD integrated with MDMA-assisted psychotherapy. The CBCT sessions, as described in Monson and Fredman's (2012) manual [1], will be integrated with elements of the Treatment Manual for MDMA-assisted Psychotherapy [2] in order to modify CBCT to incorporate MDMA as a catalyst for the therapeutic process. Sessions will be conducted by a co-therapy team and will include Preparatory Sessions, two Experimental Sessions of MDMA plus psychotherapy, and non-drug integrative psychotherapy sessions. The primary objective is to measure changes in PTSD symptoms via CAPS global severity scores in PTSD+ participants at Baseline and the Primary Endpoint, one month after the 15th CBCT session. Additional measures evaluate various qualities of the relationship between the participants.

The Experimental Sessions will last 6 to 8 hours and will be scheduled 2 weeks apart, with an intervening course of non-drug therapy. The non-drug psychotherapy includes two Preparatory Sessions prior to the first Experimental Session and five integrative CBCT sessions after each Experimental Session. Integration visits will be conducted by telemedicine (video conferencing whenever possible, telephone if there are occasions when video conferencing is not technically possible) and will include both members of the dyad. The sessions will follow a combination of the MDMA-assisted psychotherapy manual and the CBCT manual, with each method modified as needed to combine the therapies.

Table 3: Time and Events

	Screen	Preparatory		Experimental Session 1, Integrative Sessions						Midpoint	Experimental Session 2, Integrative Sessions						Primary Assess	3 Mo LTFU	6 Mo LTFU
Visit #	Pre-Study	V 1	V 2	V3	V 4	V 5	V6	V 7	V 8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Type of Session	Screening	Prep	Prep	Exp	Int	Int	Int	Int	Int	Assess /Prep	Exp	Int	Int	Int	Int	Int	Outcome	Assess	Assess
Visit Format	Telemed or Visit	Telemed	Visit	Visit (overnight)	Visit	Telemed	Telemed	Telemed	Telemed	Visit	Visit (overnight)	Visit	Telemed	Telemed	Telemed	Telemed	Telemed	Telemed	Telemed
Visit Timing Window	>1 day, month prior to Visit 1	≤ 1 Mo before V2[J]	Day 0	Day 1	Day2	Day 4	Day 6	Day 10	Day 12	Day 14	Day 15	Day 16	Day 18	Day 20	Day 24	Day 26	1 Mo post V15	3 Mo post V15	6 Mo post V15
Target Day			Fri	Sat	Sun	Tues	Thurs	Mon	Wed	Fri	Sat	Sun	Tues	Thurs	Mon	Wed			
CBCT Manual Session #			1, 2	3, 4, 5	Review	Review	6	Review	7	Review	8, 9, 10, 11	Review	12	13	14	15			
Initial Phone Screen	✓																		
Informed Consent	✓																		
Medical/Psychiatric History (Medical Record Review)	✓																		
General Phys. Exam (BP, Pulse, Temp)	✓A																		
Brief Neurological Exam	✓																		
ECG	✓																		
SCID-RV	✓																		
Clinical Lab Tests, w/ HIV, HCV test	✓A																		
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Medication Taper (if applicable)		✓																	
Study Enrollment after meeting I/E		✓	✓																
Record to Audio/Video		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Drug Screen	✓A			✓							✓								
Pregnancy Screen (if applicable)	✓A			✓							✓								
Administer IP Drug + Therapy/CBCT				✓							✓								
Integrative Therapy Session					✓	✓	✓	✓	✓			✓	✓	✓	✓	✓			
Issue Out of Session Assignments				✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓				
7 days of Telephone Contact					✓G	✓G	✓G					✓G	✓G	✓G					
CAPS[I]	✓																✓	✓	✓
PCL individual and participant	✓		✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
BDI-II	✓									✓							✓	✓	✓
IRI	✓				✓					✓		✓					✓	✓	✓
General Wellbeing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TAS-20, QRI, SORTS, CTS-2, IPF, MSIS, TABS, MDI, ERQ, PSQI, PTGI	✓									✓							✓	✓	✓
LTFU Questionnaire																		✓	✓
IPC	✓			✓C						✓	✓C						✓	✓	✓
RRPQ																	✓		
Vitals (Monitoring of BP, Pulse and Temp)				✓							✓								
Changes in Tinnitus and/or Pain [H]	✓	✓D	✓D	✓D	✓D	✓D	✓D	✓D	✓D	✓	✓D	✓D	✓D	✓D	✓D	✓D	✓	✓	✓
Subjective Units of Distress				✓							✓								
C-SSRS	✓		✓F	✓B, C, D	✓					✓	✓B, C, D	✓					✓	✓	✓
SAEs, AEs of psychiatric status or withdrawal		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AEs Requiring Medical Attention				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Spontaneously Reported Reactions				✓	✓	✓	✓			✓	✓	✓	✓	✓					
All AEs		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

A = Performed locally. B = At the beginning of the session. C = Approximately 6 hours post MDMA. D = As needed. E = Approximately every 60 minutes. F = Given post-medication washout. G = For 7 days post Experimental Session, contact will be made by phone or telemedicine and not both, C-SSRS D2 and D7 of calls only, General Wellbeing for all 7 days. H = Only in participants with pre-existing chronic pain or tinnitus. I = CAPS may be recorded to video. J = Additional time allowed if necessary for medication tapering.

4.1 Planned Duration of Study and Visit Windows

The active part of the study will take about 1 month for the dyads to complete. There are additional remote follow-up visits, 3 months and 6 months after the primary assessment. Total study participation will last about 7 months.

Screening may take place over a 1-month period; final confirmation of enrollment may be combined with the first Preparatory Session. Additional time between the first and second Preparatory Session will be allowed if necessary for medication tapering. For example, the maximum washout would be seven weeks for participants tapering off of fluoxetine plus one week for stabilization. Enrolled dyads will immediately enter the Active Group (N=10). Dyads will participate in two Preparatory Sessions, two day-long Experimental Sessions with MDMA-facilitated CBCT sessions, and Integrative Sessions following each Experimental Session in conjunction with CBCT.

The Experimental Sessions will last 6 to 8 hours and will be scheduled 2 weeks apart, with an intervening course of non-drug therapy. The non-drug psychotherapy includes two Preparatory Sessions prior to the first Experimental Session and five integrative CBCT sessions after each Experimental Session. Integration visits will be conducted by telemedicine (video conferencing whenever possible, telephone if there are occasions when video conferencing is not technically possible) and will include both members of the dyad. The sessions will follow a combination of the MDMA-assisted psychotherapy manual and the CBCT manual, with each method modified as needed to combine the therapies. Any delay between visits would result in a corresponding extension of study duration.

4.2 Recruitment and Participant Population

Participants may be persons aged 18 or older, including a PTSD+ participant who has been diagnosed with PTSD for at least 6 months and a CSO participant (i.e., intimate or non-intimate person) who does not have a current diagnosis of PTSD but is experiencing associated psychological distress as assessed by V-codes in the DSM-5. There is no upper age limit designated in this protocol as age alone does not put participants at increased risk and is a less specific exclusion criterion when compared with direct assessment of general health. Participants with medical conditions that would have contraindications to receiving MDMA would be excluded according to the Inclusion and Exclusion criteria. Participants with a history of suicide attempts will not be excluded unless risk of suicidal behavior is present at the time of the screening assessment. All participants will be evaluated by the CI to determine if there is a current risk of suicidal behavior. Participants will be enrolled according to the Inclusion/Exclusion criteria based on the clinical judgment of the CI.

The dyad members will be referred to individually as the PTSD+ participant and the CSO participant. PTSD+ participants would not be excluded for having more than one traumatic event. PTSD+ participants must have a last month CAPS score indicating at least moderate PTSD symptoms and must meet all inclusion criteria and no exclusion criteria at Baseline. CSO participants must also meet inclusion criteria and no exclusion criteria. Both participants must be in good physical health and without major medical

disorders that might affect the safety or tolerability of MDMA. Dyads will be recruited through printed ads, Internet ads, referrals from other psychiatrists, psychotherapists, or physicians, and through word of mouth. Recruitment will continue until 10 dyads that meet all inclusion criteria without meeting any exclusion criteria are enrolled. Only IRB-approved recruitment materials and advertisements will be used for the study.

4.2.1 Inclusion Criteria

Inclusion Criteria for Participants with PTSD
Individuals eligible to be enrolled into this protocol are participants who:

1. Meet DSM-5 criteria for current PTSD with a duration of 6 months or longer
2. Satisfies diagnostic criteria for PTSD using the CAPS
3. Are at least 18 years old
4. Must be generally healthy
5. Must sign a medical release for the investigators to communicate directly with their therapist and doctors
6. Are willing to refrain from taking any psychiatric medications during the study period
7. Are willing to follow restrictions and guidelines concerning consumption of food, beverages, and nicotine the night before and just prior to each experimental session
8. Are willing to be driven home the morning after the experimental sessions, after the integrative therapy session either by a driver arranged by the participant or by the site personnel or taxi and agree not to drive after each Experimental Session until the therapists deem it safe to do so
9. Are willing to commit to medication dosing, experimental sessions, follow-up sessions, to complete evaluation instruments and commit to be contacted for all necessary telephone contacts
10. Are willing to remain overnight at the study site after each experimental session until after the integrative session occurring the next morning
11. Must have a negative pregnancy test at study entry and prior to each experimental session if able to bear children, and must agree to use adequate birth control
12. Must provide a contact (relative, spouse, close friend or other caregiver other than the CSO participant) who is willing and able to be reached by the Clinical Investigators in the event of a participant becoming suicidal
13. Must agree to inform the Clinical Investigators within 48 hours of any medical conditions and procedures
14. Are proficient in speaking and reading English
15. Agree to have all clinic visit and Integrative Sessions recorded to audio and video
16. Agree to not participate in any other interventional clinical trials during the duration of this study

Inclusion Criteria for Dyad Participant
Individuals eligible to be enrolled into this protocol are participants who:

1. Are at least 18 years old
2. Meet criteria for relationship distress with partner

3. Must be generally healthy
4. Must sign a medical release for the investigators to communicate directly with their therapist and doctors
5. Are willing to refrain from taking any psychiatric medications during the study period
6. 6. Are willing to follow restrictions and guidelines concerning consumption of food, beverages, and nicotine the night before and just prior to each experimental session
7. Are willing to be driven home the morning after the experimental sessions, after the integrative therapy session either by a driver arranged by the participant or by the site personnel or taxi and agree not to drive after each Experimental Session until the therapists deem it safe to do so
8. Are willing to commit to medication dosing, experimental sessions, follow-up sessions, to complete evaluation instruments and commit to be contacted for all necessary telephone contacts
9. Are willing to remain overnight at the study site after each experimental session until after the integrative session occurring the next morning
10. Must have a negative pregnancy test at study entry and prior to each experimental session if able to bear children, and must agree to use adequate birth control
11. Must provide a contact (relative, spouse, close friend or other caregiver other than the participant with PTSD) who is willing and able to be reached by the Clinical Investigators in the event of a participant becoming suicidal
12. Must agree to inform the Clinical Investigators within 48 hours of any medical conditions and procedures
13. Are proficient in speaking and reading English
14. Agree to have all clinic visit sessions recorded to audio and video
15. Agree to not participate in any other interventional clinical trials during the duration of this study

4.2.2 Exclusion Criteria

Exclusion Criteria for Participants with PTSD
Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or are women of child bearing potential who are not practicing an effective means of birth control
2. Weigh less than 48 kg
3. Are abusing illegal drugs
4. Are not able to give adequate informed consent
5. Upon review of past and current drugs/medication must not be on or have taken a medication that is exclusionary
6. Upon review of medical or psychiatric history, must not have any current or past diagnosis that would be considered a risk to participation in the study

Exclusion Criteria for Dyad Participant
Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or are women of child bearing potential who are not practicing an effective means of birth control
2. Weigh less than 48 kg
3. Are not able to give adequate informed consent
4. Are abusing illegal drugs
5. Upon review of past and current drugs/medication must not be on or have taken a medication that is exclusionary
6. Upon review of medical or psychiatric history, must not have any current or past diagnosis that would be considered a risk to participation in the study

5.0 Methods

5.1 Measures

The following outcome, safety, and process measures will be used in the study. This study will utilize methods described in the Treatment Manual for conducting MDMA-assisted Psychotherapy combined with methods from the CBCT for PTSD manual. The integration of these manuals will provide the researcher with a consistent psychotherapy approach and test an investigational form of drug-assisted psychotherapy. The Treatment Manual is not intended to define all interactions that occur in the therapy. All psychotherapy sessions, including Experimental Sessions, may be recorded to audio and video, with all recordings preserved for research and training purposes.

Table 4: Study Measures

Measure	Purpose	Administration	Time/ # of items	When	PTSD+ Participant	CSO Participant
Screening, Inclusion & Exclusion						
SCID for DSM-5- AXIS 1 only and then screening question for AXIS 2 modules (do modules if needed)	Screening	Interview	60 minutes	Baseline	Y	Y
Primary & Secondary Outcomes						
CAPS-5 Clinician Administered PTSD Scale for DSM-5	PTSD Severity	Interview	90 minutes	Baseline, Endpoint, LTFU 3, 6	Y	N
PCL (last 24 hours) PTSD Checklist for DSM-5	PTSD symptoms	Self-report	10-15 minutes	Baseline, Integrative Sessions, Midpoint, Endpoint, LTFU 3, 6	Y	Y (PCL-Participant)
BDI-II Beck Depression Inventory	Depression Symptoms	Self-report	5-10 minutes	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
ERQ Emotional Regulation Questionnaire	Emotion regulation	Self-report	4-6 minutes	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
IRI Interpersonal Reactivity Index	Compassion empathy, social functioning	Self-report	10 minutes	Baseline, Day after Experimental Sessions, Midpoint, Endpoint, LTFU 3, 6	Y	Y
PSQI Pittsburg Sleep Quality Index	Sleep Quality	Self-report	5-10 minutes	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
PTGI Post Traumatic Growth Inventory	Growth after Trauma	Self-report	5-10 minutes	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Modified for participant. Participant will rate the PTSD participant. Y
TAS-20 Toronto Alexithymia Scale	Emotion recognition, alexithymia	Self-report	5 minutes	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
QRI Quality of Relationships Inventory	Relationship Satisfaction	Self-report	32 items	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y

Measure	Purpose	Administration	Time/ # of items	When	PTSD+ Participant	CSO Participant
SORTS Significant Others' Responses to Trauma Scale	Partner Accommodation	Self-report	40 items	Baseline, Midpoint, Endpoint, LTFU 3, 6		Y
CTS-2 (edited) Severe Items of the psychological and physical aggression subscales	Conflict Tactics and Aggression	Self-report	14 items severe, 40 items for two subscales	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
IPF Inventory of Psychosocial Functioning	Psychosocial Functioning	Self-report	80 items	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
MSIS Miller Social Intimacy Scale	Social Intimacy	Self-report	17 items	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
TABS The Trauma and Attachment Beliefs Scale	Trauma-related beliefs	Self-report	15 items	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y (modify for participant)
MDI Multiscale Dissociation Inventory	Dissociation Symptomology	Self-report	30 items, 10-15 minutes	Baseline, Midpoint, Endpoint, LTFU 3, 6	Y	Y
IPC Interpersonal Closeness Measure	Interpersonal closeness	Self-report	2-4 minutes	Baseline, During Experimental Sessions, Midpoint, Endpoint, LTFU 3, 6	Y	Y
Process Measures						
RRPQ Reactions to Research Participation Questionnaire	Process	Self-report	10 minutes	Endpoint	Y	Y
Long-term Follow-up Questionnaire	Process, Outcome, Safety	Self-Report	10-20 minutes	LTFU 3, 6	Y	Y (modify for participant)
Safety Measures						
Vitals (blood pressure, pulse, body temperature)	Safety	Medical Monitor	---	During Experimental Sessions	Y	Y
Somatic Symptoms	Outcome, Safety	Self-report	1-2 minutes	Baseline, throughout study (as needed), LTFU 3, 6	Y	Y

Measure	Purpose	Administration	Time/ # of items	When	PTSD+ Participant	CSO Participant
SUD Subjective Units of Distress	Outcome, Safety	Self-report	1 minute	During Experimental Sessions	Y	Y
C-SSRS Columbia Suicide Severity Ratings Scale	Suicidal ideation and behavior	Clinician-administered	5-20 minutes	All in-person visits, on Day2 and Day7 phone contact days after Experimental Sessions, Endpoint, LTFU 3, 6	Y	Y
General Wellbeing	General Wellbeing	Clinician-rated	1-item	All visits and phone calls	Y	Y

Baseline = During 1-month screening period prior to enrollment day. Midpoint = 2 weeks after 1st Experimental Session. Primary Endpoint = 1 month post Visit 15. LTFU 3, 6 = 3 months and 6 months after Visit 15.

5.1.1 Outcome Measures

The primary measure will be change in CAPS scores from Baseline to Primary Endpoint. A qualified, blinded IR will perform the CAPS at Baseline and outcome measurement time points. The IR will not be present during the participant's Experimental Sessions nor have any information regarding the Experimental Sessions. CAPS-5 [136] is a semi-structured clinical interview used to assess index history of DSM-5-defined traumatic event exposure [36], including the most distressing event, time since exposure, and total number of exposures, as well as frequency and severity of posttraumatic stress symptoms, as evidenced by CAPS total score. The CAPS provides diagnostic status (presence versus absence) of PTSD as well as PTSD symptom severity. Changes in the CAPS total score will be used as the primary PTSD outcome measure, and will be the primary determinant of effect size for this pilot study. All assessments, including those at Baseline, will use the CAPS assessment of symptoms over the last month. The IR will administer the CAPS at visits described in the Time and Events table either in person or via telemedicine. Studies for validation of this measure are ongoing.

The secondary measure of PTSD symptoms will be the PCL (last 24 hours), a self-report measure designed to follow DSM-5 criteria for assessing PTSD. The PTSD Checklist (PCL-5) [137] is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms, derived from the DSM-5 symptoms of PTSD [36]. Participants indicate how much distress they have experienced due to symptoms such as "Repeated, disturbing memories, thoughts, or images of a stressful experience from the past," "Trouble remembering important parts of a stressful experience from the past," and "Feeling irritable or having angry outbursts" on a five-point Likert-type scale (1 = not at all, 5 = extremely). The total PCL-5 score (a sum of all 20 items) provides an index of overall PTSD symptom severity. Reports on reliability and validation of the PCL-5 are underway; preliminary comparison with the PCL for DSM IV suggests that the cut-off for PCL-5 is 11 to 14 points lower than for the PCL [137]. Participants will complete the PCL-5 questionnaire, as specified in the Time and Events Table. The PTSD+ participant will complete it based on her or his own symptoms and the CSO participant will complete it based on the PTSD+ participant.

The BDI-II is a 1996 revision of the BDI, a 21-item self-report measure [138, 139] that will serve as a measure of depression according to DSM-IV criteria [140]. The BDI-II has been validated, has high internal consistency and good test/re-test reliability, and is not overly sensitive to daily variations in mood. It takes five to ten minutes to complete [140]. Score cutoffs indicate: 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression. Initial and subsequent studies report that the BDI-II total score has a reliability coefficient of 0.90 to 0.91 and that it is related to other measures of depression symptoms [140, 141]. Higher scores indicate more severe depressive symptoms. Both the participants will complete the BDI-II according to the Time and Events Table.

The ERQ is a brief measure of self-reported emotion-regulation. It consists of ten items that is intended to assess means of coping with emotions via changing them, as through reappraisal, or suppressing them [142]. Respondents rate indicate the extent of their agreement or disagreement with each item by selecting a point on a 7-point Likert scale,

where 1= strongly disagree and 7 = strongly agree. The ERQ should take four to six minutes to complete. Specific items are summed to produce two separate scales, Reappraisal and Suppression. The measure is reliable, with Reappraisal obtaining a Cronbach's alpha of 0.79 and Suppression an alpha of 0.73, and test-retest reliability of 0.69 [142], and scores on the ERQ are correlated with other measures of degree of emotional expressivity. The ERQ will be completed by both the PTSD+ participant and the CSO the participant according to the Time and Events table.

The IRI assesses four aspects of empathy: social functioning, self-esteem, emotionality, and sensitivity to others [143-145]. Empathy is not a discrete emotion. More accurately, empathy is a set of constructs. Therefore, the IRI accounts for the fact that each construct concerns an individual's responses to the observed experiences of other people, yet each construct is distinctive from the others. The self-report questionnaire includes 28 items that are rated on a 5-point, Likert-type scale. The four 7-item subscales include two measures of cognitive empathy and two measures of affective empathy. The internal reliabilities for the four scales range from 0.71 to 0.77, and test-retest reliabilities range from 0.62 to 0.71 [143, 144]. The IRI will be completed by both the PTSD+ participant and the CSO participant, according to the Time and Events table.

The PSQI is a measure of self-reported sleep quality over a one-month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. It consists of 19 items, with possible responses ranging from 0 to 4 on a five-point scale [146]. 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 [146, 147]. Global scores correlate with other measures of alertness and self-reported sleep quality [143]. The Pittsburgh Sleep Quality-PTSD Addendum [148] is a seven-item addendum for the PSQI that assesses disruptive nocturnal behavior specific to PTSD (e.g., hot flashes, nervousness, trauma nightmares). The PTSD+ participant will indicate the presence and severity of trauma-related sleep disturbances. Both the PTSD+ participant and the CSO participant will complete the PSQI according to the Time and Events Table.

The 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 [149, 150]. In this study, participants 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. PTGI sub-scale scores are reliable, with reliability coefficients ranging from 0.83 to 0.90, and the scale scores were moderately related to each other [149, 151]. PTGI scores are corroborated by others' assessments of posttraumatic growth, suggesting that the measure has convergent validity [152, 153]. Both the PTSD+ participant and the CSO participant will complete the PTGI according to the Time and Events Table.

The TAS-20 is a 20-item measure of self-reported difficulties with recognizing and verbalizing emotions [154, 155]. Responses are made on a 5-point Likert scale where 1 = strongly disagree and 5 = strongly agree. Estimated time of measurement is 5 to 10 minutes. The scale is comprised of three subscales; Difficulty Describing Feelings, Difficulty Identifying Feelings and Externally-Oriented Thinking, with all scales summed to create a total score reflecting presence and degree of alexithymia. The TAS-20 can be used diagnostically with a score of 61 or higher indicative of alexithymia. The TAS-20 is reliable and has good test-retest reliability (Cronbach's alpha = 0.81, test-retest of 0.77). It is an established measure of alexithymia. There is some suggestion of an overlap between this condition and Asperger's syndrome, with samples of people with Asperger's syndrome showing greater rates of alexithymia than age and gender-matched controls [156, 157]. The TAS-20 will be completed by both the PTSD+ participant and the CSO participant (modified) according to the Time and Events table.

The Quality of Relationships Inventory (QRI) is used to assess the supportive and conflictual aspects of close relationships [158]. The QRI presents an overview of approaches taken to study the social support construct. The QRI emphasizes the role of situational, intrapersonal, and interpersonal contexts in social support processes. The QRI possesses good to excellent reliability, ranging from 0.7 to 0.9 and moderate to good test-retest stability (0.48 to 0.79) [159, 160]. Both the PTSD+ participant and the CSO participant will complete the QRI according to the Time and Events Table.

The Significant Others' Responses to Trauma Scale (SORTS) [9] is a 14-item self-report measure of relationship problems and psychological distress faced by partners of people with PTSD. Each behavior or issue listed is rated on a five–point Likert scale (anchored at 0-4) for frequency of the behavior or issue and degree of distress the behavior or issue causes for the partner. The SORTS demonstrates strong internal consistency. It has Cronbach's alpha for the total scale of 0.93 and alphas of 0.86 for frequency and 0.87 for intensity (degree of distress) scores, and associations with individual and relationship distress, including a positive correlation between SORTS score and PTSD symptom severity in the partner with PTSD, and between SORTS score and depressive symptoms in the partner without PTSD. The PTSD+ participant and the CSO participant will complete the SORTS about the PTSD+ participant according to the Time and Events Table.

The Revised Conflict Tactics Scale [161] is a widely used measure of physical, psychological, and sexual aggression as well as injury and negotiation between partners. The scale consists of 39 conflict tactics, with respondents indicating the frequency with which they and their partner engage in each tactic, with each item presented as a "self" and "partner". Responses are given on a seven-point Likert scale where 0 = "This has never happened" and 6 = "More than 20 times in the past month", with 7 indicating occurrence in the past but not in the past year. The CTS2 contains four subscales; negotiation, psychological aggression, physical assault, and sexual coercion, and an injury score assessing impact of violence. CTS2 subscales are internally consistent, with alpha coefficients ranging from 0.79 to 0.95. Examining responses from relationship partners indicates high rates of agreement on responses. The CTS2 demonstrated construct validity, with scales demonstrating correlations with selected outcomes (for instance, Assault scale with injury). Research in a sample from a batterer-intervention

program found moderate to good test-retest reliability (from 0.60 to 0.79) for all scales save sexual coercion [162]. Both the PTSD+ participant and the CSO participant will complete the CTS-2 according to the Time and Events Table.

The Inventory of Psychosocial Functioning (IPF) is a self-report instrument designed to assess functional impairment across spectrum of domains. The IPF [163] is an 80-item measure that that was developed for use among individuals with PTSD. It assesses current psychosocial functioning across seven domains: romantic relationships, family, work, friendships, parenting, education, and self-care. Responses are made on a 7-point Likert scale, from "never" to "always." Summation of scores across domains yields a total score for psychosocial functioning. The IPF has excellent psychometric properties [163, 164], with Cronbach's alpha for the total scale computed at 0.93 and good internal consistency for subscales (ranging from 0.80 to 0.90) [164]. IPF subscale scores possessed positive correlations with similar scales or subscales on other measures. Both the PTSD+ participant and the CSO participant will complete the IPF according to the Time and Events Table.

The Miller Social Intimacy Scale (MSIS) is a 17-item measure of the maximum level of intimacy currently experienced. The MSIS contains six items assessing the frequency of intimate contact and 11 items addressing intensity of contact, with all responses given on an 10-point Likert scale, with the total score assessing a single factor [165]. The MSIS can be used to measure social intimacy for people referring to an opposite sex or a same sex person and intimacy in close friends or romantic partners [166]. The MSIS is reliable, with Cronbach's alpha ranging from 0.84 to 0.95 [165, 166] and MSIS scores were positively related to scores on another measure of social intimacy [165]. Both the PTSD+ participant and the CSO participant will complete the MSIS according to the Time and Events Table.

The Trauma and Attachment Beliefs Scale (TABS) was developed as a brief self-report measure of maladaptive beliefs about current life circumstances that may occur following trauma exposure [167]. The measure consists of 15 items, with responses made on a seven-point Likert scale with 1 = not at all true for you and 7 = completely true for you. This scale assesses maladaptive beliefs within three domains: (a) threat of harm, (b) self-worth and judgment, and (c) reliability and trustworthiness of others. After following procedures for reverse-scored items, scores are summed to produce scale scores for each domain. The TABS has an overall reliability of alpha of 0.82, with scale reliability ranging from 0.71 to 0.76. TABS scores exhibit a positive association with CAPS global severity scores, particularly for the Threat of Harm scale, and the scale had a negative association with scores on the PTGI. Both the PTSD+ participant and the CSO participant will complete the TABS according to the Time and Events Table. The CSO participant will complete a modified version.

The Multiscale Dissociation Inventory (MDI) is a 30-item self-report test of dissociative symptomatology in the last month, with responses made along a five-point Likert scale, with 1 = never and 5 = very often. It is fully standardized and normed, and measures six different type of dissociative response: disengagement, depersonalization, derealization, emotional constriction / numbing, memory disturbance, and identity dissociation. A total dissociation score can also be calculated. Reliability for each subscale various from 0.74

for memory disturbance to 0.91 for derealization. The MDI has been found to have good psychometric qualities in both the normative and validation samples [168-170]. Both the PTSD+ participant and the CSO participant will complete the MDI according to the Time and Events Table.

The measure of state interpersonal closeness (IPC) is a 5-item non-verbal sponsor-developed self-report measure. Participants are asked to draw on a sheet of paper "how close you feel right now" to the self as observed, the Clinical Investigators, a selected significant other and "the world." Distance in mm between the self and each target will be considered an indirect measure of interpersonal closeness. The measure is expected to take between 2 and 4 minutes to complete. Both the PTSD+ participant and the CSO participant will complete the measures of interpersonal closeness according to the Time and Events Table.

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 participant safety throughout the study. Both the PTSD+ participant and the CSO participant will be assessed according to the Time and Events Table.

5.1.2 Safety Measures

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

Safety measures, including vital signs and a measurement of psychological distress, will be assessed during all Experimental Sessions. Participants 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 participant safety during Experimental Sessions. Both the PTSD+ participant and the CSO participant will complete the SUD according to the Measures and Time and Events Table.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [171]. It consists of a "Baseline" form that assesses lifetime suicidal ideation, ideation intensity, and behavior and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions, and can be administered during a face-to-face interview or over the telephone. Suicidal ideation and behavior will be assessed at Baseline, during most face-to-face visits, during the second and seventh days of telephone contact, and after each Experimental Session. Participants who are discontinuing medication to participate in the study will complete the C-SSRS before and after medication washout. The C-SSRS Intensity scale for Lifetime obtained a Cronbach's alpha of 0.93 and 0.94 for the Since Last Visit form, and Last Visit C-SSRS severity scores were positively correlated with the BDI "suicide thoughts" item [172]. Both the PTSD+ participant and the CSO

participant will complete the C-SSRS according to the Measures and Time and Events Table.

Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure, body temperature, and pulse will be measured at the outset of the Experimental Session, once prior to administration of the supplemental dose, and at the end of the Experimental Session, or until it returns to near baseline levels. The timing of these measurements will be adjusted so they do not interfere with the therapeutic process. Blood pressure will be measured more frequently if there are symptoms, such as chest pain, shortness of breath or neurological symptoms or any other signs or symptoms that may be indicative of a medical complication.

A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain [173-175]. 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 [174, 176-178]. 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 [174, 177, 178]. Both the PTSD+ participant and the CSO participant will be evaluated for Somatic Symptoms.

All AEs and spontaneously reported reactions will be collected, as described in Section 8.5. AEs and spontaneously reported reactions may be collected during face-to-face visits or over the telephone. Common reactions that are spontaneously reported are collected for seven days after each Experimental Session on a separate CRF page and will be categorized as mild, moderate, or severe. The researchers will ask participants about thoughts about killing or harming themselves at these visits and during the second and seventh day of telephone contact with the study therapists.

5.1.3 Process Measures

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

The Reactions to Research Participation Questionnaire (RRPQ) [179] is an assessment of causes for taking part in research and responses to the experience of being a research participant. The RRPQ is intended to assess the participants' experiences as research participants, perceived reasons for consenting to be a research participant and perceived freedom to take part in the study. This will be completed by the PTSD+ participant and the CSO participant according to the Time and Events table.

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 Visits. Both the PTSD+ participant and the CSO participant will complete the Long-term Follow-up Questionnaire according to the Time and Events Table. The CSO participant will complete a modified version.

5.2 Study Procedures and Visit Descriptions

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

Prospective dyads will be prescreened by telephone according to an IRB-approved script to learn if they meet basic eligibility criteria. Each dyad that is prescreened should be assigned a screening number, and recorded on the Screening Log where information on the selection of potential participants in the trial should be collected.

Upon the PTSD+ participant and the CSO participant signing the IRB-approved informed consent form (ICF), the potential dyad may commence study-related screening activities. The screening numbers should also be recorded on the signed ICF. If a dyad is enrolled, the study staff should record the enrollment date and assign dyad numbers. If a dyad is not enrolled, an explanation should be recorded on the Screening Log. If a CSO participant fails to qualify for the study, potential PTSD+ participants may nominate a different support participant. A CRF will not be completed for dyads that are not enrolled. These dyads will only be documented on the Screening Log and source records. It is the responsibility of the Clinical Investigator to file the Screening Log and the Dyad Identification Code List 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 one month prior to enrollment. Screening visits may be conducted by telemedicine, phone, or in person. Screening may take up to one month, with the Baseline CAPS being conducted no more than 8 weeks before the first Experimental Session, leaving room for appropriate medication washout of at least five half-lives of pre-study psychiatric medications and active metabolites, plus one week for stabilization.

If the CAPS is completed outside of this window for a participant, the PI should consult the 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 8 weeks. If, after reviewing all information, the PI concludes that the PTSD+ participant and CSO participant are eligible, they will enroll in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

a. Explain and obtain written informed consent from the PTSD+ participant and CSO participant. Written informed consent must be obtained prior to performing any tests or evaluations for the study.
b. Assign the dyad 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 Clinical Investigator for the treatment period of the study.
d. Qualified study staff will obtain medical and psychological history by interview for both the PTSD+ participant and CSO participant
e. Qualified study staff will administer the lifetime C-SSRS at baseline to assess suicide risk for both the PTSD+ participant and CSO participant
f. General Wellbeing will be assessed for both the PTSD+ participant and CSO

participant.

g. Qualified study staff will collect information on pre-study and current medications for both the PTSD+ participant and CSO participant
h. A physician will perform a general physical examination for both the PTSD+ participant and CSO participant. 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 state law. The clinical laboratory values will be used to establish eligibility and will be kept with the participant's source record. The clinical laboratory values will not be captured in the CRF, but will be used to establish eligibility and will be kept with the participant's source record. Clinically significant abnormal values will be captured as medical history. If, upon examination, there are questions raised about possible medical problems, the study physician will request a review of participant medical records and request additional tests or assessments as indicated.

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

- Structured Clinical Interview for DSM-5 Diagnoses (Research Version) (SCID-RV) to assess eligibility based on Axis I diagnoses, which includes a self-report questionnaire to focus on modules to use based on symptoms for both the PTSD+ participant and CSO participant
- SCID-II Axis 2 questionnaire to determine if specific modules of the SCID-II Interview will be conducted to confirm diagnoses of personality disorders
- Last-month CAPS for the PTSD+ participant to assess PTSD symptoms and eligibility, which may be recorded to video in as many instances as necessary to establish inter-rater reliability

The following self-report measures will be completed:

- PTGI (in reference to time since the trauma) for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- PCL-5 (last 24 hours to assess) to assess PTSD symptoms for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant.
- TABS to assess trauma related beliefs for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- MDI to assess dissociative symptomology for the PTSD+ participant and CSO participant
- SORTS to assess partner accommodation for the PTSD+ participant and CSO participant
- BDI-II to assess depression symptoms for both the PTSD+ participant and CSO participant
- PSQI to assess sleep quality for both the PTSD+ participant and CSO participant. PSQI-PTSD Addendum will be assessed for the PTSD+ participant only
- ERQ to assess emotional regulation for both the PTSD+ participant and CSO participant
- TAS-20 to assess emotion recognition, alexithymia for both the PTSD+ participant and CSO participant
- QRI to assess relationship satisfaction for both the PTSD+ participant and CSO participant
- CTS to assess conflict, tactics and aggression for both the PTSD+ participant and CSO participant
- IPF to assess psychosocial functioning for both the PTSD+ participant and CSO participant
- MSIS to assess social intimacy for both the PTSD+ participant and CSO participant
- IRI to assess compassion, empathy and social functioning for both the PTSD+ participant and CSO participant
- IPC for both the PTSD+ participant and CSO participant

5.2.2 Preparatory Psychotherapy Session (Visit 1 - Telemedicine Visit)

(Less than 4 weeks prior to Visit 2)

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

a. Complete a final review of inclusion/exclusion criteria
b. Assess General Wellbeing
c. Confirm eligibility and willingness to participate in study
d. Enroll participant and issue dyad number
e. Ensure medical history and medication history is complete. After enrollment new events will be collected as AEs and new medications, as described in Sections 8.0 and 9.0.

f. Discuss medication tapering, if applicable. Upon confirmation of eligibility, the PI or another designated study physician will consult the prescribing physician to initiate medication tapering for the PTSD+ participant and the CSO participant, if applicable, who must refrain from taking a psychiatric medication for the study. The prescribing physician's opinion aboiut medication discontinuation will documented either in writing from the prescribing physician, or in writing by the study physician documenting phone contact with the prescribing physician. Tapering will follow a time course appropriate for the medication given its half-life, with the first Experimental Session scheduled to occur after complete washout. Individuals using opiates for pain management will be asked to decrease the dose or avoid taking their pain medication for 24 hours prior to Experimental Sessions if possible, as these medications may reduce the efficacy of MDMA. Participants will be permitted to take their prescribed opiate medication during this period if necessitated by pain flare-ups.

This first Preparatory Session will last 90 minutes and take place at Visit 1. During the Preparatory Sessions:

a. This visit may be conducted by telemedicine or phone.
b. Therapists may record all sessions to audio and video. The PTSD+ participant and the CSO participant will be given access to review audio or video recordings from the sessions upon request.
c. The therapists will inquire about any possible changes in the PTSD+ participant's or CSO participant's health to ensure that eligibility criteria is met and if applicable, will confirm that the PTSD+ participant and CSO participant have appropriately tapered off of medications.
d. The PTSD+ participant, CSO participant, and therapists will discuss goals for the Experimental Session and will complete preparatory psychotherapy. Preparatory sessions will promote a safe setting for confronting trauma-related memories, emotions, and thoughts.

5.2.3 Preparatory Psychotherapy Session (Visit 2 - Clinic Visit)

(Day 0 - Friday)

CBCT Manual Sessions 1 and 2

Sessions 1 and 2 – Psychoeducation about PTSD and safety building for the relationship.

This second Preparatory Session will last 90 minutes and take place at Visit 2. During the Preparatory Session:

a. Therapists may record all sessions to audio and video. The PTSD+ participant and CSO participant will be given access to review audio or video recordings from the sessions upon request.
b. Collect AEs and Medications, as described in Sections 8.0 and 9.0
c. Confirm that the PTSD+ participant and CSO participant have appropriately tapered off of medications.

d. Assess General Wellbeing
e. Qualified study staff will administer the C-SSRS
f. The PTSD+ participant, CSO participant, and therapists will discuss goals for the Experimental Session and will complete preparatory psychotherapy. Preparatory sessions will promote a safe setting for confronting trauma-related memories, emotions, and thoughts.
g. Give the Reminder of Study Rules to the dyad, which includes instructions and restrictions for conduct prior to receiving the drug. The PTSD+ participant and CSO participant must agree to:
    - Ingest only alcohol-free liquids after 24:00 (midnight) the evening before the Experimental Session
    - Refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each Experimental Session
    - Not use caffeine or nicotine for two hours before and six hours after ingesting the drug, or until therapists deem it safe to do so

5.2.4 Experimental Sessions (Visits 3 and 10 - Overnight Stay)

(Days 1 and 15- Saturdays)

CBCT Manual Sessions 3, 4, and 5 and 8, 9, 10, and 11

Sessions 3, 4, and 5 – Beginning of satisfaction enhancement and undermining avoidance. Specific content related to listening and approaching, and sharing of thoughts and feelings.

Sessions 8, 9, 10, and 11 – Making meaning of the trauma. Discussion of the themes of acceptance, blame, trust, and control.

Table 5. Schedule of Procedures for Experimental Sessions

Approximate Time	Procedure or Action
9:00	Urine drug screen and pregnancy test, participant acclimated to environment, C-SSRS
9:45	Baseline BP, BT, Pulse, SUD
10:00	**MDMA Administration**, Begin video recording
11:00	SUD
11:30	BP, BT, SUD, Pulse, **Administer optional supplemental dose**
12:30	SUD
14:00	SUD
As needed	BP, BT, Pulse
Every 60-90 minutes	SUD
Approximately six hours after drug administration	C-SSRS, General Wellbeing, BP, BT, Pulse

The PTSD+ participant and CSO participant will receive two Experimental Sessions of open-label MDMA-assisted psychotherapy in conjunction with CBCT scheduled two weeks apart. Procedures for MDMA-assisted psychotherapy in conjunction with CBCT will remain the same across all sessions, and all procedures will be the same.

Pre-drug:

a. On the day of the Experimental Session, the PTSD+ participant and CSO participant will arrive approximately 60 to 90 minutes prior to drug administration.
b. Confirm continuing eligibility by reviewing inclusion/exclusion criteria including medications and adverse events.
c. Perform a urine drug screen. A positive drug screen will be reviewed by the Clinical Investigator and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study.
d. If a woman is of childbearing potential, perform a urine pregnancy test. A positive pregnancy screen is cause for withdrawal from the protocol.
e. If the dyad continues to meet criteria and the dyad reports that they followed appropriate rules and restrictions, the session will proceed.
f. Review procedures for the Experimental Session with the dyad.
g. Record the entire session to video and audio. Dyads will be given access to review audio or video recordings of their Experimental Sessions upon request.
h. The session will last for approximately eight hours or longer, followed by an overnight stay at the study site.
i. The therapists will administer the C-SSRS to the dyad prior to drug administration.
j. Before drug administration, discuss and review the dyad's goals, intentions and concerns and some of the commonly experienced effects of MDMA.
k. Instruct the dyad not to use caffeine or nicotine two hours before or six hours after the dose of drug.
l. PTSD+ participant and CSO participant body temperatures will be measured at Baseline and according to Table 4. The therapists may make more frequent measurements if body temperature exceeds more than 1oC above Baseline.
m. The PTSD+ participant and CSO participant will complete the SUD at Baseline prior to initial dose administration. The PTSD+ participant 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.
n. Measure blood pressure and pulse at Baseline prior to the Experimental Session, and according to Table 4 thereafter. More frequent measures will be taken if clinical signs and symptoms of hypertension are observed.

During:

o. At approximately 10:00 in the morning, participants will receive the initial dose of drug along with a glass of water.
p. The PTSD+ participant and CSO participant will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided if the PTSD+

participant or CSO participant wishes to use them. The PTSD+ participant and CSO participant may speak to the therapists whenever they wish, who will provide guidance and support as needed. CBCT therapy will be administered during the session according to the CBCT Manual.

q. After the first hour, if the PTSD+ participant or CSO participant has not spoken spontaneously, check in with that participant about the nature of the experience. For the rest of the experience, as appropriate, the therapists will support and encourage the PTSD+ participant in emotional processing and resolution of whatever psychological material is emerging as described in the treatment manual.
r. Record any spontaneously reported reactions during the session.
s. Provide water and electrolyte containing fluids throughout the session but not to exceed 3L overall.
t. An optional supplemental dose of MDMA half the amount of the initial dose may be administered approximately 1.5 to 2 hours after the initial dose unless contraindicated.
u. Administer the self-report IPC for both the PTSD+ participant and the CSO participant.
v. Provide food during the latter part of the session.
w. If it is appropriate to do so, initiate the first question of the C-SSRS at any point in the session if the PTSD+ participant or CSO participant 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.
x. Assess General Wellbeing for both the PTSD+ participant and the CSO participant.
y. End the session if all medical and psychiatric parameters are acceptable and the PTSD+ participant and the CSO participant are alert, ambulatory, and emotionally stable.

Post-drug:

z. Give the dyad the Out of Session Assignments to be completed after the end of the Experimental Session and returned the next day at the Integrative Session.
aa. The therapists will depart the site when they have concluded that the participants are emotionally and medically stable. Therapists and the study physician shall remain available to participants during the Experimental Session and for one week after via 24-hour cellular phone for integration as needed.
bb. Spontaneously reported reactions, AEs, and Medications will be collected, as described in Sections 8.0 and 9.0.

The PTSD+ participant and the CSO participant will remain overnight in an appropriately furnished room at the study site. An attendant will check in periodically on the dyad during the overnight stay. The attendant will monitor the PTSD+ participant's and the CSO participant's condition and will help the dyad relax during the overnight stay. The attendant will be an individual with some previous training in managing psychological distress, and will be thoroughly briefed by study staff about their role as an attendant who

is available and supportive but not intrusive. If there is an emergency or the PTSD+ participant or the CSO participant needs additional support, the attendant can contact the therapists. The dyad 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. The dyad will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

5.2.5 Integrative Sessions 24 Hours after Experimental Session (Visits 4 and 11 - Clinic Visit)

(Day 2 and 16 - Sundays)

CBCT Manual Sessions Review

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

Generally, these sessions include discussing material that emerged during Experimental Sessions and helping dyad integrate their experiences both internally and into daily life. Therapists will validate the choices of the participant 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 participants' level of emotional stability and state of emotional and physical wellbeing. Therapists will emphasize their commitment to support the participants during the integration period and will be available via phone for additional meetings if needed. The dyad will be encouraged to relax and rest as much as possible for several days after the Experimental Session.

During integrative psychotherapy sessions:

a. The integrative psychotherapy session will be recorded to audio and video when possible. Participants will be given access to review audio and video of the session upon request.
b. The therapists will administer the C-SSRS during each Integrative Session.
c. Discuss and review events that occurred with the dyad during the Experimental Session, including thoughts, feelings, and memories. If necessary, the therapists will help the participants to reduce any residual psychological distress they are experiencing. The therapists will also encourage reconnection with any feelings of acceptance, intimacy, and reduced fear experienced in Experimental Sessions, and reflection about integrating those experiences into their relationships and everyday lives. The therapists will be supportive, validating the experience and facilitating understanding and emotional clearing.
d. The therapists will remain accessible any time the participants need support outside the scheduled Integrative Sessions.
e. Assess the PTSD+ participant's mental health and the presence of any remaining reactions during integrative psychotherapy immediately after each Experimental Session.
f. Integrative psychotherapy sessions can also serve as an opportunity for the therapists to gather information about the effects of the drug on the PTSD+

participant in an unstructured manner.

g. Assess General Wellbeing for both the PTSD+ participant and CSO participant.
h. Administer the self-report PCL-5 (last 24 hours to assess) to assess PTSD symptoms for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant.
i. Administer the self-report IRI to assess compassion, empathy, and social functioning for both the PTSD+ participant and CSO participant.
j. After the integrative psychotherapy sessions, a person previously selected by the dyad will provide a ride home. If the dyad are unable to locate an individual willing or able to take them home, or if the designated person is unable to assist due to unforeseen events, the therapists will aid the dyad in finding an alternative means of returning home.
k. Spontaneously reported reactions, AEs and Medications will be collected, as described in Sections 8.0 and 9.0.
l. Give the dyad the Out of Session Assignments to be completed after the end of the Integrative Session and returned to the study staff by the next visit.
m. Remind the participants that they will have daily contact by phone or during telemedicine visits for the next seven days.

5.2.5 Daily Telephone Contact for Seven Days after an Experimental Session

During daily phone contact:

a. Starting on the day of the integrative psychotherapy session following each Experimental Session, one of the therapists will contact the PTSD+ participant and CSO participant via telephone, telemedicine, or in person every day for one week. The goal of daily contact is assessment of changes in General Wellbeing, safety, and offering support.
b. The telephone contact will be for a brief check-in lasting five to 15 minutes, or as long as necessary to address any participant's concerns and to assess participants' wellbeing. Additional telephone contact can be initiated at the request of the therapists or participant.
c. On the second and seventh day of contact after the Experimental Session, the therapists will administer the C-SSRS.
d. General Wellbeing will be assessed at each phone call.
e. Spontaneously reported reactions, AEs and Medications will be collected, as described in Sections 8.0 and 9.0.

5.2.6 Integrative Psychotherapy Between Experimental Sessions (Visits 5, 6, 7, 8, 12, 13, 14, and 15 - Telemedicine Visits)

(Days 4, 6, 10, 12, 18, 20, 24, and 26)

CBCT Manual Sessions Review, 6, 7, 12, 13, 14, and 15

Sessions 6 and 7 – Getting UNSTUCK (learning the process of dyadic cognitive restructuring) and problem solving.

Sessions 12, 13, 14, and 15 – Making meaning of the trauma. Discussion specifically of themes of emotional closeness, physical closeness, posttraumatic growth, and review and reinforcement of treatment gains.

After each Experimental Session, in addition to the session the following morning, the PTSD+ participant and CSO participant will have four additional integrative psychotherapy sessions with the therapists lasting 90 minutes each. The therapists may conduct more sessions if they and the PTSD+ participant deem it necessary.

Generally, 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 PTSD+ participant during the integration period and will be available via phone or pager. Dyads will be encouraged to relax and rest as much as possible for several days after the Experimental Session.

During integrative psychotherapy sessions:

a. These visits may be conducted by telemedicine or phone.
b. Record each Integrative Session to audio and video. Dyads will be given access to review one or more Integrative Sessions upon request.
c. The C-SSRS will be administered just prior to beginning each Integrative Session.
d. General Wellbeing will be assessed at each Integrative Session.
e. The PTSD+ participant and therapists will continue to work on supporting the PTSD+ participant as they consider their experiences during Experimental Sessions.
f. Assess General Wellbeing for both the PTSD+ participant and CSO participant.
g. Administer the self-report PCL-5 (last 24 hours to assess) to assess PTSD symptoms for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant.
h. Give the dyad the Out of Session Assignments to be completed after the end of the Integrative Session and returned by the next visit. (Except Visit 15).
i. The therapists will use clinical judgment to assess the PTSD+ participant'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 PTSD+ participant or CSO participant may also initiate contact with the therapists at any time throughout the study.
j. Collect AEs and medications, as described in Sections 8.0 and 9.0.

5.2.7 Evaluation and Preparation Visit at Midpoint (Visit 9 - Clinic Visit)

(Day 14 - Friday)

CBCT Manual Sessions Review

The midpoint evaluation will occur 13 days after the first Experimental Session. Dyads who have withdrawn from treatment but have continued for follow-up will also complete this time point. This session will be recorded to audio/video.

a. The therapists will assess suicidal ideation and behavior with the C-SSRS
b. General Wellbeing will be assessed
c. Collect AEs and medications, as described in Sections 8.0 and 9.0

The following self-report measures will be completed at the midpoint:

- PTGI (in reference to time since the trauma) for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- PCL (last 24 hours to assess) to assess PTSD symptoms for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- TABS to assess trauma related beliefs for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- MDI to assess dissociative symptomology for the PTSD+ participant and CSO participant
- SORTS to assess partner accommodation for the PTSD+ participant and CSO participant
- BDI-II to assess depression symptoms for both the PTSD+ participant and CSO participant
- PSQI to assess sleep quality for both the PTSD+ participant and CSO participant. PSQI PTSD addendum will be completed by PTSD+ participant only
- ERQ to assess emotional regulation for both the PTSD+ participant and CSO participant
- TAS-20 to assess emotion recognition, alexithymia for both the PTSD+ participant and CSO participant
- QRI to assess relationship satisfaction for both the PTSD+ participant and CSO participant
- CTS to assess conflict, tactics and aggression for both the PTSD+ participant and CSO participant
- IPF to assess psychosocial functioning for both the PTSD+ participant and CSO participant
- MSIS to assess social intimacy for both the PTSD+ participant and CSO participant
- IRI to assess compassion, empathy and social functioning for both the PTSD+ participant and CSO participant
- IPC for both the PTSD+ participant and CSO participant

5.2.8 Primary Assessment (Visit 16 – Telemedicine Visit)

(30 days post Visit 15)

The PTSD+ participant and CSO participant will repeat all outcome measures with the IR and meet with the therapists again 30 days after Visit 15. This visit may consist of two

meetings that may be completed on separate days, one with the IR and the other with the therapists. Session may be recorded to audio/video.

a. The therapists will assess suicidal ideation and behavior with the C-SSRS
b. General Wellbeing will be assessed
c. Last-month CAPS for the PTSD+ participant only will be performed to assess PTSD symptoms, which may be recorded to video in as many instances as necessary to establish inter-rater reliability
d. Collect AEs and medications, as described in Sections 8.0 and 9.0

The following self-report measures will be completed at the outcome assessment:

- PTGI (in reference to time since the trauma) for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- PCL (last 24 hours to assess) to assess PTSD symptoms for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- TABS to assess trauma related beliefs for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- MDI to assess dissociative symptomology for the PTSD+ participant and CSO participant
- SORTS to assess partner accommodation for the PTSD+ participant and CSO participant
- BDI-II to assess depression symptoms for both the PTSD+ participant and CSO participant
- PSQI to assess sleep quality for both the PTSD+ participant and CSO participant PSQI PTSD addendum will be completed by PTSD+ participant only
- ERQ to assess emotional regulation for both the PTSD+ participant and CSO participant
- TAS-20 to assess emotion recognition, alexithymia for both the PTSD+ participant and CSO participant
- QRI to assess relationship satisfaction for both the PTSD+ participant and CSO participant
- CTS to assess conflict, tactics and aggression for both the PTSD+ participant and CSO participant
- IPF to assess psychosocial functioning for both the PTSD+ participant and CSO participant
- MSIS to assess social intimacy for both the PTSD+ participant and CSO participant
- IRI to assess compassion, empathy and social functioning for both the PTSD+ participant and CSO participant
- IPC for both the PTSD+ participant and CSO participant
- RRPQ to assess the process for both the PTSD+ participant and CSO participant

5.2.9 Long-term Follow-up (Visits 17 and 18 – Telemedicine Visits)

(3 months and 6 months post Visit 15)

The PTSD+ participant and CSO participant will be evaluated for long-term effects 3 months and 6 months after their last MDMA-assisted psychotherapy with CBCT session. This visit will consist of two meetings, one with the IR and the other with the therapists via telemedicine. PTSD+ participants and CSO participants who have withdrawn from treatment but have continued for follow-up will also complete these time points. At the Long-term Follow-up Visits:

a. The therapists will assess suicidal ideation and behavior with the C-SSRS.
b. General Wellbeing will be assessed.
c. Last-month CAPS for the PTSD+ participant will be performed to assess PTSD symptoms, which may be recorded to video in as many instances as necessary to establish inter-rater reliability.
d. Collect AEs and medications, as described in Sections 8.0 and 9.0.

The following self-report measures will be completed at the outcome:

- PTGI (in reference to time since the trauma) for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- PCL-5 (last 24 hours to assess) to assess PTSD symptoms for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- TABS to assess trauma related beliefs for the PTSD+ participant and modified for the CSO participant to rate the PTSD+ participant
- MDI to assess dissociative symptomology for the PTSD+ participant and CSO participant
- SORTS to assess partner accommodation for the PTSD+ participant and CSO participant
- BDI-II to assess depression symptoms for both the PTSD+ participant and CSO participant
- PSQI to assess sleep quality for both the PTSD+ participant and CSO participant. PSQI PTSD addendum will be completed by PTSD+ participant only
- ERQ to assess emotional regulation for both the PTSD+ participant and CSO participant
- TAS-20 to assess emotion recognition, alexithymia for both the PTSD+ participant and CSO participant
- QRI to assess relationship satisfaction for both the PTSD+ participant and CSO participant
- CTS to assess conflict, tactics and aggression for both the PTSD+ participant and CSO participant
- IPF to assess psychosocial functioning for both the PTSD+ participant and CSO participant
- MSIS to assess social intimacy for both the PTSD+ participant and CSO participant
- IRI to assess compassion, empathy, and social functioning for both the PTSD+ participant and CSO participant
- IPC for both the PTSD+ participant and CSO participant
- Long-term Follow-up Questionnaire to assess the process, outcome and safety for the PTSD+ participant and modified foe the CSO participant

5.3 Participant Numbering

Prior to enrollment, the dyad will be tracked with two sets of initials and a screening number assigned sequentially starting at "S001". Dyads who meet all inclusion and no exclusion criteria will be enrolled into the study and will be assigned a five-digit participant number. The first two digits will be " 01" or "02" and will identify the PTSD+ participant versus the CSO participant. The next three digits identify the dyad within the site and will be assigned sequentially, with 001 corresponding to the first dyad enrolled, e.g. the first enrolled dyad will be 01001 and 02001 and the second dyad will be 01002 and 02002, etc.

5.4 Removal of Participants from the Study

Participants can withdraw consent at any time without prejudice. The therapists can withdraw a participant if, in their clinical judgment, it is in the best interest of the dyad or if the participant cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If the therapists withdraw a dyad from the study, the therapists will explain the reason for withdrawing the dyad. The reason for early termination will be recorded in both the PTSD+ participant's and the CSO participant's source records and CRF. If one person in the dyad wishes to withdraw, both participants will be dropped from treatment.

Participants will be clinically monitored after withdrawal, the cause of which will be recorded in their 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 PI and/or sponsor.

If a participant develops any exclusion criteria that in the opinion of the Medical Monitor, affects the safety of either member of the dyad, including psychiatric diagnosis, pregnancy or excluded medications, the PTSD+ participant will discontinue treatment but remain in the study for follow-up purposes. Whenever possible, the tests and evaluations listed for the Midpoint, Outcome, and 3-month and 6-month follow-up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the Clinical Investigators, Medical Monitor, and/or sponsor. Dyads who discontinue treatment will not be replaced.

5.5 Premature Discontinuation of the Study

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

6.0 Investigational Product

6.1 Description of Active Compounds

The investigational product to be used in this protocol is MDMA. This ring-substituted phenylisopropylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor [180-182]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower. See Section 2.2.3 and the IB for more information on the investigational product.

6.2 Preparation and Administration

In this study, 10 dyads will receive MDMA in an open-label fashion.

6.2.1 Doses

Table 6. Treatment Condition

Treatment Group	1st Experimental Session Dose	2nd Experimental Session Dose
Active MDMA-assisted Psychotherapy (N=10 dyads)	75 mg MDMA + optional 37.5 mg supplement	100 mg MDMA + optional 50 mg supplement or 75 mg MDMA + optional 37.5 mg supplement

6.2.2 Compounding

MDMA in bulk will be sent from a Schedule 1 licensed storage facility to the Drug Enforcement Agency (DEA) Schedule I license holder for the study. The Schedule I license holder will oversee compounding by a pharmacist. The pharmacist will provide bulk lactose for compounding MDMA capsules. The pharmacist will weigh the MDMA into doses of 75 mg, 100 mg, 50 mg, and 37.5 mg (calculated as the weight of the hydrochloride salt) and place it in gelatin capsules with lactose. Capsules for the initial dose will be clearly differentiated from capsules used for the supplemental dose. The encapsulation will be performed by a pharmacist who has the appropriate skills.

6.2.3 Labeling

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, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with federal and state 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 PTSD+ participant and CSO participant per Experimental Session. The sponsor monitor will oversee the process of drug packaging conducted by the pharmacist.

Figure 1. Examples of Drug Labels

Holding Box Labels:

Holding Box Label

MAPS Study: MPVA-1
Investigational Product: MDMA
Dose: X mg
Lot #: XXX
Administer as per protocol
Caution: Limited by Law to Investigational Use Only

Primary Container Outer Labels:

Container Label

MAPS Study: MPVA-1
Open Label
100 mg + 50 mg MDMA
Lot #: XXX
Container #: XXX

Dyad #: _____
Experimental Session #: _____
Administer as per protocol - Investigational Use Only

Container Label

MAPS Study: MPVA-1
Open Label
75 mg + 37.5 mg MDMA
Lot #: XXX
Container #: XXX

Dyad #: _____
Experimental Session #: _____
Administer as per protocol - Investigational Use Only

Primary Container Inner Labels:

Open Label
INITIAL DOSE 75 mg
Dyad #: _____Experimental Session #: ___

Open Label
SUPPLEMENTAL DOSE 37.5 mg
Dyad #: _____Experimental Session #: ___

Open Label
INITIAL DOSE 100 mg
Dyad #: Experimental Session #:

Open Label
SUPPLEMENTAL DOSE 50 mg
Dyad #: Experimental Session #:

Initial doses will be distinguished from supplemental doses through labeling them to ensure that the correct dose is administered at the scheduled time. Each dose of MDMA will be administered along with a glass of water or electrolyte-containing fluid. MDMA will be administered in the same manner during each Experimental Session.

6.3 Drug Accountability

Forms will be provided to track drug accountability and administration throughout the study. Drug accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all state and federal regulations and forms pertaining to the use of controlled substances, and forms will be maintained by the Schedule 1 License Holder.

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.

6.4 Drug Storage and Handling

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

IP will only be removed for a single Experimental Session at a time and will be administered orally at the treatment site. 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 for the second Experimental Session. The dose to be used at the second session is at the discretion of the CI.

The Schedule 1 License Holder will dispense the appropriate container number for each Experimental Session. If an optional dose is not administered, the unused capsules will be kept in their respective inner envelopes inside of the primary container in the safe for drug accountability.

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

6.5 MDMA Stability

Complete details on the chemistry, manufacturing, and control of the MDMA to be used are described in Drug Master file (DMF) # 6293. As described in that file, MDMA was prepared for human consumption in 1985 by David Nichols, Ph.D. at the Department of Medicinal Chemistry and Pharmacology at Purdue University. The identity and purity of this MDMA was confirmed using High Performance Liquid Chromatography (HPLC) in 1997 as described in DMF # 6293 and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor prior to starting MAPS' first U.S. pilot study of MDMA-assisted psychotherapy in people with PTSD. The analysis found the MDMA to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart on February

2006, continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9% pure. This MDMA is currently in use in an ongoing investigation of MDMA-assisted psychotherapy in the U.S., was also used in MP-1 with drug administration ending in 2008, and it was also used in a non-sponsor supported study in 2006 [183].

7.0 Risks of Participation

7.1 Risks and Discomforts Associated with Psychotherapy Sessions and Assessment of Measures

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

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

7.2 Risks of Receiving MDMA

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

impaired gait/balance, and sensitivity to cold were more often reported by participants in the MDMA than the placebo condition, and irritability was slightly more likely to be reported in the placebo condition. Additionally, participants in the MDMA condition were more likely to report muscle tension in various body parts and diarrhea.

These effects are transient and diminish as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, needing more sleep, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects are reported less often than acute effects. More information on spontaneously reported reactions is described in the IB.

MDMA may produce mild alterations in sensory perception and altered perception of time [10, 109, 184]. Women may be more sensitive to these effects [15]. 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 [185]. For this reason, participants 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 users, can be found in the sponsor's Investigator Brochure.

7.2.1 Safety Plan and Procedures for Participants Who Screen Positive for Suicidal ideation or Intent

The CI will minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with a history of suicide attempts will not be excluded unless risk of suicidal behavior is present at the time of the screening assessment. Participants will be enrolled according to the Inclusion/Exclusion criteria based on the clinical judgment of the CI.

After enrollment, data on General Well Being will be collected at each visit on the participant's current demeanor and state of mind and risk of deterioration. Participants will be telephoned on a daily basis for the first week after each experimental session to assess General Wellbeing, safety, and offer support.

The CI or qualified designee will administer the CSSRS according to the Time and Events table, and as needed depending on clinical presentation of the participants, to monitor for development and intensity of suicidal ideation and/or behavior. The therapist will implement the following plan to assess elevated or imminent suicide risk.

If the Since Last Visit CSSRS reveals current serious Suicidal Ideation (Scores of 4 or greater), indicating risk at the time of the assessment, or positive Suicidal Behavior

(Scores of 1 or greater) then the participant will be referred for further management as described below.

1. If the participant has current suicidal ideation, but no specific plan to commit suicide (Suicidal Ideation Score = 4), the therapist administering the CSSRS will ensure:
    a. Participants are evaluated by the investigators to determine appropriate course of action and will discuss the findings with the participant and their personal therapist, if applicable.
    b. Regular check-ins via phone or in person will be continued until the participant has stabilized or a new course of action is taken based on changes in CSSRS score and/or ongoing clinical assessment.
    c. If this finding is treatment-emergent and clinically significant, the event will be collected as an Adverse Event.
    d. Treatment would be continued when deemed appropriate by the CI and Medical Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up.

2. If the participant has suicidal ideation, and a plan to commit suicide (Suicidal Ideation Score = 5) or positive Suicidal Behavior (Score greater than or equal to 1), the therapist administering the CSSRS will assess whether the risk is imminent. A Suicidal Ideation score of 5 does not necessarily indicate an immediate risk if the thoughts are fleeting, fairly easily controlled, and deterrents are strong. If there is no imminent risk, the therapist will follow the procedure described in number 1. If there is imminent risk of suicidal behavior, the therapist will ensure:
    a. Participants are evaluated to determine appropriate course of action, and the study therapist will contact their personal therapist or come to the study site for a visit, depending on their location.
    b. If it is determined that the participant is at imminent risk of suicide, the CI or qualified staff member will do one of the following:
        1) Escort the participant to the Emergency Department;
        2) Escort the participant to an appropriate mental health services facility (e.g.hospital psychiatric unit); or
        3) call 911 and ensure that the participant is transferred to the responding medical personnel.
    c. If the participant will not comply and wishes to leave without consultation, call 911. Explain that the participant is in immediate danger of committing suicide. Provide a complete description of the participant and give any other needed details to ensure the participant's safety.
    d. Notify appropriate members of the study team and Sponsor representatives.
    e. If this finding is treatment-emergent and clinically significant, the event will be collected as an Adverse Event and the seriousness will be evaluated. SAEs will be reported per FDA guidance.
    f. Treatment would be continued when deemed appropriate by the CI and Medical Monitor, unless it is determined that treatment should be

discontinued, in which case the participant will enter follow-up.

7.2.2 Cardiovascular and Sympathomimetic Effects

The highest dose to be employed in this study, the active dose of 100 mg, followed by a supplemental dose of 50 mg after 1.5 to 2.0 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 participants and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity. For more information, see the sponsor's Investigator Brochure.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing hypertension and monitoring blood pressure and pulse, as described in Section 5.1.2. During Experimental Sessions the co-therapists will continually evaluate the patient for signs or symptoms of a developing hypertensive or other cardiovascular emergency. Participants reporting chest pain, shortness of breath or neurological symptoms or other potential indicators of hypertensive emergency or any other serious medical problem will have more frequent measurements and assessment by the study physician. Any participant who experiences medical complications during an Experimental Session will not be given another Experimental Session unless it is approved by the Clinical Investigator, study physician and the Medical Monitor.

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

The study physician will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). The therapists will attend to any signs or symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress, and will notify the study physician if this occurs for on-site evaluation or a decision to initiate transfer to the ED. If any participant has neurological deficits, as assessed by the study physician, whether or not they are associated with hypertensive crisis, they will receive oxygen and vital signs and general condition will be closely monitored pending transfer to the hospital. 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 [186, 187].

The therapists will observe the participants and note any complaints of chest pain. If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, they will receive heart rhythm monitoring, oxygen and will be monitored as described above. If necessary, they will be transported to the ED or a location in the hospital where appropriate care can be given. They will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the participant has had an 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 [188].

7.2.3 Psychological Distress

Mild anxiety and depressed mood are occasionally reported one to three days after MDMA administration [13, 15, and see the IB]. Psychological distress from MDMA could arise at any time from the first indications of drug effects until the last effects have dissipated (approximately three to five hours after drug administration), or even later. Any anxiety or distress occurring 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-assisted session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting, and have responded well to reassurance from the therapists, with occasional use of benzodiazepines for anxiety. In this study, participants will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties participants 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 participants for the period of a week after the Experimental Session
- Providing non-drug integrative psychotherapy sessions
- Participants 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 participants.

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, participants will be made aware of the fact that difficult emotions, including grief, rage and fear or panic, may arise during Experimental Sessions. Every effort will be made to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the Experimental Session, including empathic listening on the part of the therapists and performance of diaphragmatic breathing or other stress inoculation techniques by participants.

At the end of the six to eight-hour Experimental Session, if the PTSD+ participant or CSO participant is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

- If the PTSD+ participant or CSO participant is anxious, agitated, in danger of any self-harm or is suicidal at the end of the Experimental Session, the therapists will remain with them for at least two more hours. During this time, the therapists will employ affect management techniques, will talk with the participant to help them gain cognitive perspective of their experiences, and will help them implement the self-soothing and stress inoculation techniques presented during the Preparatory Session. If this situation should occur during an integrative therapy session, at least one of the therapists will be available to stay with the person for at least two additional hours.
- If a PTSD+ participant or CSO participant remains severely anxious, agitated or in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period, the Clinical Investigator will decide between the following options:
    1. A psychiatric nurse, therapeutic assistant, physician, or therapist will stay with the PTSD+ participant or CSO participant until the time of their appointment with the therapists the next day. The therapists will then meet with the participant daily until the period of destabilization has passed.
    2. If a PTSD+ participant or CSO participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an MDMA-assisted session, the study physician may prescribe a rescue medication such as a benzodiazepine, zolpidem, or other anxiolytic or sedative according to the physician's clinical judgment. This medication will be captured on the concomitant medications CRF page. The physician should not prescribe an SSRI, SNRI or MAOI in this context unless it has been determined that the participant 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 PTSD+ participant or CSO participant should become psychotic arrangements will be made to stabilize them and transfer them to the ED if necessary.

PTSD+ participants or CSO participants hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the Clinical Investigators will carefully evaluate their emotional status.

For those PTSD+ participants or CSO participants engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the outside therapists will be involved in the management of any psychiatric complications. For those PTSD+ participant or CSO participants engaged in an ongoing psychotherapeutic relationship with the Clinical Investigators, the management of any psychiatric complications will be undertaken by them in their capacity as therapists.

7.2.4 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [15] and ambient temperature does not enhance or attenuate this slight elevation in humans.

If temperature rises more than 1°C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5°C above Baseline despite these efforts, the study physician will be consulted for further evaluation and treatment.

7.2.5 Reproductive and Developmental Risks

Risks posed by MDMA to pregnant women are not known. One of two studies of Ecstasy users suggests that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [189, 190], and a third reported some developmental delays in mothers reporting use of and other drugs during pregnancy [191] as discussed in the IB.

Pregnant and lactating women will be excluded from participation in the study, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session and must agree to use birth control for the treatment portion of the study.

7.2.6 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [192]. 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, 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 [193]. We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. More information on the potential neurotoxicity of MDMA can be found in the IB.

7.2.7 Risk Mitigation

Careful review of medical screening data will be utilized to exclude potential participants 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. Participants will not be allowed to drink more than 3L of fluids over the course of the Experimental Session, and fluid intake will be spread out appropriately during the session. Fluids administered will include electrolytes. If a participant exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an Experimental Session, they will not be given another Experimental Session unless it is approved by the Clinical Investigator, study physician, and the Medical Monitor.

7.3 Abuse Liability

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

Whether MDMA-assisted psychotherapy will cause some PTSD patients to develop an MDMA use disorder 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 participant took Ecstasy after completing the study and failed to reproduce the experience from the study, and a number of participants 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 participants took Ecstasy outside of the study during the long-term follow-up period.

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

8.0 Adverse Events

8.1 Adverse Events

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

An unexpected adverse event is one that is not listed in the current IB or an event that is by nature more specific or more severe than a listed event.

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

The severity of events reported on the "Adverse Events" CRF will be determined by the study physician as:

- Mild: no limitation in normal daily activity
- Moderate: some limitation in normal daily activity
- Severe: unable to perform normal daily activity

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

1. Not Related: the AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the participant's pre-existing condition.
2. Possibly Related: the administration of the investigational product and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product.
3. Probably Related: exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

8.2 Spontaneously Reported Reactions

Commonly expected spontaneously reported reactions are collected on a separate CRF page and will be categorized as mild, moderate, or severe. Common, expected reactions are defined as those most frequently reported in the literature and include: Anxiety, Diarrhea, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Heavy Legs, Impaired Gait/Balance, Impaired Judgment, Increased Irritability, Insomnia, Jaw Clenching or Tight Jaw, Lack of Appetite, Low Mood, Muscle Tension, Nausea, Need More Sleep, Nystagmus, Parasthesias, Perspiration, Restlessness, Rumination (increased private worries), Sensitivity to Cold, Thirst, and Weakness. Spontaneously reported reactions will be collected during the Experimental Session and the seven days of telephone contact following the Integrative Session that occurs on the day after each Experimental Session. Each reported reaction will be actively followed during follow-up phone calls or visits until resolution. Any reported event that is not listed as a Spontaneously Reported Reaction will be collected as an Adverse Event following the plan in Section 8.5. Any common reaction lasting longer than seven days will be tracked as an adverse event in order to obtain a resolution date.

8.3 Serious Adverse Events

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

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

AEs that do not fall into these categories are defined as non-serious. It should be noted that a severe adverse event need not be serious in nature and that a SAE need not, by definition, be severe.

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

8.4 Medical Emergencies

The sessions will be conducted in a private practice setting, 3.3 miles away from the East Cooper Medical Center where emergency equipment is immediately available. The study physician will be available in the case of medical emergencies and will be within three miles away from the study site during Experimental Sessions. The therapists or study physician will be available via mobile phone or pager throughout the study if any problem occurs when a PTSD+ participant or CSO participant is not at the site, and they will continue to see their outside therapist as needed throughout the study. For a recently completed Phase 2 trial, the sponsor has established contingency plans for responding to those AEs that appear most likely, based on a comprehensive review of literature described in the current IB. Similar contingency plans will be used in this protocol. The site will provide an Automated External Defibrillator (AED). The at least one therapist on each team will maintain BLS certification.

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

8.5 Adverse Event Collection

The study physician will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The therapists will collect AEs during study/telemedicine 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 Clinical Investigator's awareness of their occurrence. All SAE reports should be faxed to the sponsor. A fax number will be provided to the site in separate site-specific instruction for SAE reporting. In addition to the fax, the study physician, Clinical Investigator, or designee should call the CRA during normal working hours and verbally inform the CRA of the SAE. During off business hours or if medical advice is needed immediately please call the sponsor Medical Monitor. An SAE reporting instruction with all contact numbers will be provided to the site prior to study start.

Medical Monitor:

Julie Holland, M.D.

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 participant termination
- All AEs and spontaneously reported reactions will be collected on the day of drug administration and for seven days after each Experimental Session
- Any spontaneously reported reactions that have not resolved to the PTSD+ participant's or CSO participant's Baseline level of severity after seven days will be collected on the Adverse Event Report page until resolution
- Events requiring medical attention will be collected from enrollment through the PTSD+ participant's or CSO participant's last 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 participants on the last visit prior to the 3-month follow-up to record information on medications taken to treat SAEs, AEs leading to withdrawal and psychiatric AEs during the follow-up period. The memory aid card will not be collected, but information from the card will be used to aid the participants in providing information to the Clinical Investigator. This information may be collected by phone.

9.0 Concomitant Medications and Tapering Instructions

If the PTSD+ participant or CSO participant is being treated with psychiatric drugs at the time they are recruited into the study, the prospective PTSD+ participant and CSO participant will be encouraged to discuss medication tapering with their outside treating physician, if any, and will be required to give the PI 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 Experimental Session to avoid the possibility of any drug-drug interaction (the interval will be at least five times the particular drug and active metabolites' half-life, plus one week for stabilization).

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

All medications, over the counter (OTC) and prescription will be collected from screening through seven days after the last MDMA-assisted session. From seven days after the last MDMA-assisted session through Study Termination only prescription or OTC medications taken to treat AEs will be collected. Throughout the protocol all medications used to treat AEs will be collected, as described in Section 8.5, and all changes including discontinuations or additions to psychiatric medications will be collected. Medications will be recorded on the concomitant medications CRF.

In general, any MAOi will require a washout of at least 14 days or five half-lives of the medication or active metabolite (whichever is greater) plus one week for symptom stabilization. The Medication Tapering Table now includes phenelzine, an example MAOi, (half life of 11.6 hours) with a minimum of 14-day washout as requested. However, this table is not exhaustive. The washout time for any drug not listed on the table will be at least 5 times the half life of the drug or active metabolite as published in the package insert, plus 1 week for symptom stabilization.

PTSD+ participants and CSO participants must be willing to refrain from taking any psychiatric medications during the active portion of the study with the exception of gabapentin when prescribed for pain control. If a participant 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. Individuals using opiates for pain management will be asked to decrease the dose or avoid taking their pain medication for 24 hours prior to

Experimental Sessions if possible, as these medications may reduce the efficacy of MDMA. Participants will be permitted to take their prescribed opiate medication during this period if necessitated by pain flare-ups.

Table 7. 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
phenelzine	Nardil	11.6	14
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 PI 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.

PTSD+ participants and CSO participants must agree that, for one week preceding the MDMA-assisted 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)

PTSD+ participants and CSO participants will receive a memory aid card to record information at the 3-month and 6-month follow-up, as described in Section 8.5. PTSD+ participants will use this card to record changes in psychiatric medications that they will be asked about at the Study Termination Visit. Memory aids will not be collected. PTSD+ participants may return to taking psychiatric medications and discontinue birth control after the Primary Endpoint if necessary.

10.0 Clinical Laboratory Assessments

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

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

- Serum electrolytes and metabolic profile
    - ALT/SGPT
    - Albumin:globulin (A:G) ratio
    - Albumin, serum
    - Alkaline phosphatase, serum
    - AST/SGOT
    - Bilirubin, total
    - BUN:creatinine ratio
    - Calcium, serum
    - Carbon dioxide
    - Chloride, serum
    - Creatinine, serum
    - Globulin, total
    - Glucose, serum
    - Potassium, serum
    - Protein, total, serum
    - Sodium, serum
- CBC
    - Hematocrit
    - Hemoglobin
    - MCV
    - MCH
    - MCHC
    - RDW
    - Percentage and absolute differential counts
    - RBC
    - Red blood cell count
    - White blood cell count
- Urinalysis
    - Color
    - Appearance
    - Specific gravity

  - pH
  - Protein
  - Glucose
  - Ketones
  - Occult blood
  - Leukocyte esterase
  - Nitrite
  - Bilirubin
  - Urobilinogen
- Thyroid function
  - TSH high sensitivity
  - Free T4
  - Free T3
- HIV serology
- Urine-dip pregnancy test for females of childbearing potential
- Urinary drug test will be performed

Any national LabCorp laboratory may perform assessments other than the urine drug screen and pregnancy test.

11.0 Study Monitoring, Auditing, and Documentation

The Clinical Investigator, therapists, and their study staff will be trained prior to the start of the study. The study site will be monitored by site visits and telephone calls to the Clinical Investigator by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment in order to comply with GCP guidelines and to ensure validity of the study data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. Electronic CRFs supplied by the sponsor will be completed for each participant enrolled. Monitoring and auditing procedures will be supplied in a separate document.

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

12.0 Data Analysis

Key Personnel, MAPS, and the biostatistician will agree on a Statistical Analysis Plan at the beginning of the study. The biostatistician will perform an Intent to Treat (ITT) analysis using repeated measures Analysis of Covariance (ANCOVA) to compare demographics and all available data from any participant receiving at least one Experimental Session and completing follow-up assessments from all participants, even if they withdraw from the allocated treatment prior to the Primary Endpoint.

This pilot study will test the impact of MDMA-assisted psychotherapy with CBCT for reducing PTSD and other psychological symptomology (e.g., depression) among a sample (N=10) of participants with PTSD. The primary measure will be a paired T-test of

CAPS scores from Baseline to Primary Endpoint. In addition, to determine the strength of the treatment effect, pre to post (paired) mean differences effect size estimates will be calculated. Durability of effects will be examined by comparing changes from Baseline to the assessments at three and six months after the final Experimental Session using mixed-effects regression methods, which accounts for both missing data and the nesting of correlated longitudinal data within participants.

Effect sizes will be estimated for all outcome measures using Cohen's (1988) procedures (Cohen's d and small sample bias corrected Hedges' g) [194]. Effects on depression symptoms, psychological functioning, trauma-related beliefs, interpersonal closeness, and sleep quality will also be assessed for exploratory purposes. The biostatistician will conduct secondary analyses of self-report assessments using repeated measures ANCOVA. As a secondary outcome measure, weekly PCL-S assessments will be conducted 15 times, starting at the second prep visit, weekly during treatment, and three follow-up assessments. To examine changes in PCL-S over the 15 time points, the sponsor statistician will use linear mixed-effects regression with restricted maximum likelihood estimation, using weeks as a continuous variable. Measures of relationship satisfaction will be analyzed separately for participants with and without PTSD. Statistical significance will be determined based on $\alpha < .05$ for all tests other than the PCL-S, which will be a secondary measure for self-reported PTSD symptoms intended to support the CAPS.

Qualitative safety analyses will examine adverse events, concomitant medications, and spontaneously reported reactions by summary tables listing maximum severity and duration, as well as frequencies and percentages, tabulated overall and by PTSD+ participants and CSO participants. Quantitative safety analyses will examine vital signs, changes in Tinnitus and/or Pain, SUD, and C-SSRS, with comparisons made between by PTSD+ participants and CSO participants for effect of PTSD on safety measures.

12.1 Statistical Power

This pilot RCT is the first study of its kind intended to establish preliminary effect size estimates of CBCT combined with MDMA-assisted psychotherapy for PTSD. In the absence of published effect sizes for this new treatment modality, effect sizes were estimated based on prior trials of these individual treatments. In a limited number of small pilot studies, CBCT for PTSD yielded paired-treatment effect sizes of $g > 1.0$ for improvements in PTSD on the primary outcome measure and co-morbid symptoms. The two completed controlled RCTs of MDMA-assisted psychotherapy for PTSD have yielded effect sizes of $g > 1.0$ for improvements in PTSD symptoms as well. Assuming that effect size of the combined treatment may be approximately 0.8, estimated power for a within-subject analysis with a significance level of .05 based on a 2-tailed test, is 62% for a sample size of 10 participants for the primary measure, suggesting the potential for an underpowered design, but with some possibility of detecting a within-subject effect due to treatment. Statistical power estimates were not available for secondary and exploratory measures, as they were previously not used in sponsor-supported studies.

13.0 Ethics

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

The protocol and the ICF must be reviewed and approved by a properly constituted IRB and FDA before study start. Signed and dated documentation of IRB and FDA approvals must be provided to the sponsor. Prior to study start, the Clinical Investigator is required to sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor.

14.0 Informed Consent

The main licensed therapists are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the participant into the trial. Information about the study must be given orally and in an understandable form. Written information about the trial will also be provided. The informed consent discussion must be conducted by a person who is qualified according to FDA regulations. The PTSD+ participants and CSO participants should have the opportunity to inquire about details of the MDMA-assisted session and to consider participation.

For all PTSD+ participants and CSO participants the dose of MDMA will be disclosed. This is not a blinded study.

In addition to the explanation of study visits, the information should include that access to original medical records and processing of coded personal information must be authorized. Written consent to take part in the study includes giving the Clinical Investigators permission to view the PTSD+ participant's and CSO participant'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 PTSD+ participants and CSO participants 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 PTSD+ participant and CSO participant source documents. The therapists will provide a copy of the signed ICF to the dyad and will maintain the original in the ISF.

The written ICF and any other written information to be provided to PTSD+ participants and CSO participants should be revised whenever important new information becomes available that may be relevant to the dyad's consent. Any revised ICF and written information should receive approval from an IRB before use. The PTSD+ participant and CSO participant 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.

PTSD+ participants and CSO participants can withdraw consent at any time without prejudice. If a PTSD+ participant or CSO participant withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the Clinical Investigators will have full access to the PTSD+ participant's or CSO participant's medical records, including Study Termination Visit information. If only the HIPAA authorization is revoked, the Clinical Investigators will have full access to all of the medical records prior to the date and time of revocation.

15.0 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of PTSD+ participants and CSO participants in their role as research participants. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. Except for the screening log, the ICF, and a participant contact information sheet that will be stored separately from other documents, all data will be identified only by the participant's initials on the source document and five-digit participant number. If past medical records are needed, participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. Copies of audio and video recordings intended for sharing with participants will only be marked with the PTSD+ participant's and CSO participant's participant number. Any materials mailed to PTSD+ participants and CSO participants will be sent along with stamped return envelopes using the office address of the Clinical Investigator both as main and return address. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the Clinical Investigators directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

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

16.0 Costs to Participants

There will be no costs to the study participants for any study-related procedures. The sponsor will cover all costs of study participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of the PTSD+ participant'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 PTSD+ participant or to the participant directly. It is anticipated that there will not be any charges for treatment that is unrelated to the study except in the case of participants who

previously received therapy from the Clinical Investigator and who will continue to receive ongoing treatment that is not related to participating in the study.

17.0 Treatment and Compensation for Study-Related Injury

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

18.0 Record Retention

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

19.0 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 PI 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 PI is 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 PI 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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