MPVA-1 Statistical Analysis Plan

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CORPORATION DESIGNEE	Amy Emerson Executive Director and Director of Clinical Research
USE	In conjunction with relevant FDA guidance
STUDY TITLE	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)**
LATEST PROTOCOL	Amendment 4 Version 1, May 8, 2017
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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)
CSI	Couples Satisfaction Index
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
MMRM	Mixed Effect Model Repeat Measures
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)
SAP	Statistical Analysis Plan
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
TEAE	Treatment Emergent Adverse Events
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

1.0 Introduction

This document presents a Statistical Analysis Plan (SAP) for MAPS study protocol MPVA-1, a Phase 1/2 open-label feasibility study exploring the safety and efficacy of combined MDMA-assisted pyschotherapy with Cognitive-Behavioral Conjoint Therapy (CBCT) for treating individulas with chronic treatment-resistent Posttraumatic Stress Disorder (PTSD) and a significant other with associated pyschological distress. This study is not intended to lead to a registration study.

The statistical plan described hereafter is an *a priori* plan based on the statistical analysis plans included in the study protocol. This SAP will be finalized prior to any inferential or descriptive analyses of data pertaining to the MAPS-sponsored MPVA-1 study. SAS programming may occur as study data accumulate in order to have analysis programs ready at the time data are locked and available for analysis. For the reasons stated here, the conduct of the study in the field is considered to be independent of any study outcomes that might materialize upon enactment of the currently proposed statistical plan.

2.0 Background

This is a feasibility and method development study to examine combining CBCT and MDMA-assisted psychotherapy in subjects with chronic PTSD (PTSD+ participant) and a Concerned Significant Other participant (CSO participant) without a current PTSD diagnosis but with related psychological distress. Eligible and enrolled participants will undergo a 2-month treatment course in dyads that includes CBCT, as described in Monson and Fredman's (2012) manual [1], integrated with elements of the Treatment Manual for MDMA-assisted psychotherapy to guide the incorporation of CBCT and MDMA [2]. This study will serve as a guide for reseasrchers to test the feasibility of two therapeutic doses of MDMA: (a) 75 mg + optional 37.5 mg supplement in Experimental Session 1 and (b) 100 mg + optional 50 mg (default dose) or 75 mg + optional 37.5 mg supplement in Experiemntal Session 2, plus psychotherapy sessions and non-drug CBCT sessions for PTSD (Tables 1& 2). The initial active doses are expected to produce all the commonly reported effects of MDMA, including changes in affect, mood, cognition, feelings of interpersonal closeness, and trust. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects expected after the initial dose. Each therapy team will have one therapist professionally trained and experienced in MDMA-assisted psychotherapy and the other therapist in CBCT. Whenever possible both therapists will have had training in both methods.

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

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

The purpose of this study is to test the feasibility of combining MDMA-assisted psychotherapy with CBCT in participants diagnosed with PTSD and their partners. Results from this study will serve as preliminary data to design a larger study to examine the safety and efficacy of this new treatment.

3.0 Study Objectives

Primary Objective

The primary objective of the study is to assess changes in PTSD symptoms as measured by CAPS-5 in PTSD+ participants from Baseline to the Primary Endpoint.

3.2 Exploratory Objectives

Secondary and other 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.

<u>PTSD+ Participants Only</u>

- Assess changes in PTSD symptoms from baseline as measured by the CAPS-5 in participants with chronic PTSD at Long-term Follow-up at 3 months and 6 months.

<u>CSO Participants Only</u>

- 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 the CSO participant.

<u>PTSD+ Participants and CSO Participants</u>

- 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 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 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 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 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 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 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.

Relationship Outcomes

- 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 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 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 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.
- Assess changes in couples satisfaction from baseline with the Couples Satisfaction Index (CSI) at the Midpoint, Primary Endpoint, and Long-term Follow-up at 3 months and 6 months for both participants if romantically involved.

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, AEs, 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 Table 3: Time and Events.
- 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

As background for the statistical methods presented below, this section provides an overview of the study design. This overview is a summary only. The protocol is the definitive reference for all matters discussed in what follows.

This is a Phase 1/2 open-label study to examine the feasibility of combined MDMA-assisted psychotherapy with CBCT in 10 dyads that include one participant who has been diagnosed with PTSD for at least 6 months (PTSD+ participant) and a CSO participant (i.e., intimate or non-intimate partner who does not have a current diagnosis of PTSD). 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 2-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, 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. Sessions will be conducted by a co-therapy team and will include Preparatory Sessions, two Experimental Sessions of MDMA plus psychotherapy, and non-drug CBCT psychotherapy Integrative 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. (See Time and Events Table).

The Experimental Sessions will last 6 to 8 hours and will be scheduled 3 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 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 (See Time and Events Table).

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	4 visits over 3 weeks between V3 and V10				~3 weeks post V3; prior to V10	~3 weeks post V3	1 day post V10	4 visits over 4 weeks between V10 and V15				1 Mo post V15	3 Mo post V15	6 Mo post V15
CBCT Manual Session #			1, 2, 3	4, 5 – Condensed delivery just after MDMA administration	Review	6	7	8	9	10, 11	Review	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 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, CSI	✓									✓							✓	✓	✓
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 after administration of MDMA.

D = As needed.
E = Approximately every 60 minutes.
F = Given after medication washout.
G = For 7 days after 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.

5.0 Measures

5.1 Outcome Measures

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

PTSD Checklist for DSM-5 (PCL): last month, since last visit, since last week

Beck Depression Inventory-II (BDI-II)

Emotional Regulations Questionnaire (ERQ)

Interpersonal Reactivity Index (IRI)

Pittsburgh Sleep Quality Index (PSQI)

Post Traumatic Growth Inventory (PTGI)

Toronto Alexithymia Scale (TAS-20),

Quality of Relationships Inventory (QRI)

Significant Others' Responses to Trauma Scale (SORTS)

Revised Conflicts Tactics Scale (CTS2)

Inventory of Psychosocial Functioning (IPF)

Miller Social Intimacy Scale (MSIS)

The Trauma and Attachment Beliefs Scale (TABS)

Multiscale Dissociation Inventory (MDI)

Interpersonal Closeness Measure (IPC)

Couples Satisfaction Index (Romantic couples only) (CSI)

5.2 Process Measures

Reactions to Research Participation Questionnaire (RRPQ)

Long-term Follow-up Questionnaire (LTFUQ)

5.3 **Safety Measures**

Vitals (blood pressure, pulse, body temperature)

Somatic Symptoms

Subjective Units of Distress (SUD)

Columbia Suicide Severity Rating Scale (C-SSRS)

General Well-being (GWB)

Spontaneously Reported Reactions (SRR)

Adverse Events (AEs)

6.0 Analyses

In general, nominal variables will be described in terms of frequencies and percentages and analyzed using chi square analysis. Ordinal and non-normal continuous variables will be described using sample median and range, and analyzed by non-parametric statistical tests, and approximately normal variables will be described using sample mean and standard deviations and analyzed by parametric statistical tests. All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. All p-values will be rounded to and displayed in four decimals. P-value less than 0.0001 will be shown in tables as <0.0001. For any analysis that is called out as parametric, e.g. t-test, the parametric assumptions will be examined. If necessary, nonparametric analyses will be utilized, e.g. Wilcoxon rank-sum test.

Clinical data will be presented in tabular format. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings. Analyses will be carried out with SAS Version 9.4 (or higher). Selected results may be presented graphically using standard graphical software.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified as such in the final clinical study report.

Analysis Populations

Modified Intent-to-treat (mITT): all dyads that received at least one experimental session and completed at least one outcome assessment

Per protocol (PP): all dyads that completed two experimental sessions and primary outcome assessment, and did not experience a major protocol deviation

Safety: all subjects who received any study treatment

Handling of Dropouts, Missing Data

Dyads who discontinue treatment prior to completing the second experimental session and the primary endpoint will be replaced. These dropout subjects will be asked to complete an outcome assessment prior to continuing to the long-term follow-up.

Early termination visit data for mITT and Safety variables will be analyzed at the closest scheduled visit after the last experimental session completed. If the closest visit has valid data, the early termination data will be assigned to the next available visit. If a dyad discontinues and does not participate in an early termination visit, data from the last available visit will be used to replace the missing early termination visit data.

Partial or Missing Dates:

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then:

   i) If the year matches the first dose date year, then impute the month and day of the first dose date.

   ii) Otherwise, assign 'January.'

3) If the day is unknown, then:

   i) If the month and year match the first dose date month and year, then impute the day of the first dose date.

   ii) Otherwise, assign the first day of the month.

B. Stop Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then assign 'December.'

3) If the day is unknown, then assign the last day of the month.

Protocol Deviations

All protocol deviations will be included as a categorized listing. Safety and mITT analyses will include all enrolled dyads with all available data. Dyads with major deviations will be excluded from the per protocol analyses. Possible protocol deviations include the following seven categories:

- Subject entered study but did not meet criteria
- Subject developed withdrawal criteria but was not withdrawn
- Subject received excluded concomitant treatment
- Protocol procedure not performed per protocol
- Subject received incorrect treatment or incorrect dose
- Protocol procedure performed out of range
- Miscellaneous

The number of dyads in each protocol deviation category listed below will be summarized by MDMA group, and individual subjects will be listed in the appendix.

Pooling of Investigator Centers

All subjects in this study come from one investigational center.

Baseline Values

Baseline values are from screening/baseline visit for all measures, except CAPS-5 and C-SSRS. Baseline CAPS-5 will be assessed, during screening (pre-study), no more than 8 weeks before the first experimental session. This allows adequate washout of at least five half-lives of pre-study psychiatric medications and active metabolites, plus one week for stabilization. If CAPS-5 is completed outside of this window for a participant, the PI will consult the CRA and Medical Monitor to determine if the Baseline CAPS should be repeated. For C-SSRS, pre-enrollment scores will be used as a measure of 'lifetime' suicidal ideation and behavior, and preparatory session 2 (visit 2) prior to drug administration will used as 'baseline.' If a subject was not administered the C-SSRS at preparatory session 2 (visit 2), then 'baseline' scores will be visit 3 pre-drug C-SSRS observation.

Subject Disposition and Dosing Summary

All subjects enrolled in the study (i.e., who sign informed consent and complete inclusion/exclusion criteria) will be included in the summary of subject disposition and accountability. No inferential statistical tests will be performed. The tabulation of number of subjects will be displayed for all subjects in the Safety population, in the mITT population, and

in the PP population. The number and percent of subjects who completed or discontinued the study will be reported along with reasons for early termination. Percents will be defined as the number of participants who completed, or number discontinued, over the total number of subjects in the total study sample, and separately, for PTSD+ participants and CSO participants. The timepoint of doses and total MDMA (mg) administered will be summarized for the Safety, mITT and PP populations for the total sample and by PTSD+ participants and CSO participants.

Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be summarized descriptively overall and by PTST+ participants and CSO participants. The demographic data and baseline characteristics will be summarized for the mITT.

Prior and Concomitant Medications

The number and percent of subjects who took medications prior to and after signing informed consent will be summarized descriptively for the total sample and by PTSD+ participants and CSO participants. Concomitant medications will be summarized similarly. Prior and concomitant medications will be summarized for the Safety Population. Psychiatric medications will be coded to common drug classes and terms.

Efficacy Analyses

For all primary, secondary, and exploratory endpoints descriptive statistics (n, mean, standard deviation, median, range, effect size (for measures of interest), or frequencies and percentages where appropriate) will be provided for the total sample and by PTSD+ participants and CSO participants.

Effect size (Hedges' *g*) will be determined by calculating the mean difference pre- and post-treatment divided by the pooled weighted standard deviations for means at baseline and follow-up [3].

$$\text{Hedges' } g = (M_1 - M_2) / SD^*_{pooled}$$

Where:

- $M_1 - M_2$ = difference in means
- SD^*_{pooled} = pooled and weighted standard deviations

1. Primary Efficacy Analyses

The primary efficacy evaluation is a paired t-test of CAPS-5 Total Severity scores at baseline and the primary endpoint (visit 16) at an alpha level of 0.05. If the parametric assumptions for t-test analyses are not met, the analogous nonparametric methods will be used (Wilcoxon Rank-Sum).

2. Secondary and Exploratory Efficacy Analyses

Efficacy of secondary and other exploratory outcome measures will be assessed at baseline, midpoint (visit 9), and primary endpoint (visit 16) to examine change in scores over time in the total sample, and separately, by PTSD+ participants and CSO participants.

For each model, a one-way repeated-measures ANOVA with post-hoc contrast comparisons will be conducted to test the effects of the treatment on: PTSD CAPS-5; Significant Others' Responses to Trauma Scale (SORTS); Posttraumatic Stress Disorder Checklist for the DSM-5 (PCL-5); Beck Depression Inventory-II (BDI-II); Emotion Regulation Questionnaire (ERQ); Pittsburgh Sleep Quality Index (PSQI); Posttraumatic Growth Inventory (PTGI); Toronto Alexithymia Scale-20 (TAS-20); Inventory of Psychosocial Functioning (IPF); Revised Conflict Tactics Scale (CTS-2); Trauma and Attachment Beliefs Scale (TABS); and Multiscale Dissociation Inventory (MDI). Relationship distress outcome measures include: Interpersonal Reactivity Index (IRI); Quality of Relationships Inventory (QRI); Miller Social Intimacy Scale (MSIS); Interpersonal Closeness Measure (IPC); and Couples Satisfaction Index (CSI).

3. Secondary Efficacy Analyses at Secondary Endpoints (Long-Term Follow-up)

Efficacy of outcome measures for long-term follow-up will be assessed at baseline, midpoint (visit 9), primary endpoint (visit 16), 3-month follow-up (visit 17), and 6-month follow-up (Visit 18) to examine changes over time in the total sample, and separately, by PTSD+ participants and CSO participants.

For each model, a one-way repeated-measures ANCOVA with baseline scores as covariates and post-hoc contrast comparisons will be conducted to test the effects of the treatment on: PTSD CAPS-5; Significant Others' Responses to Trauma Scale (SORTS); Posttraumatic Stress Disorder Checklist for the DSM-5 (PCL-5); Beck Depression Inventory-II (BDI-II); Emotion Regulation Questionnaire (ERQ); Pittsburgh Sleep Quality Index (PSQI); Posttraumatic Growth Inventory (PTGI); Toronto Alexithymia Scale-20 (TAS-20); Inventory of Psychosocial Functioning (IPF); Revised Conflict Tactics Scale (CTS-2); Trauma and Attachment Beliefs Scale (TABS); and Multiscale Dissociation Inventory (MDI). Relationship distress outcome measures include: Interpersonal Reactivity Index (IRI); Quality of Relationships Inventory (QRI); Miller Social Intimacy Scale (MSIS); Interpersonal Closeness Measure (IPC); and Couples Satisfaction Index (CSI).

If data is missing from participant dropouts a mixed effect model repeat measures (MMRM) will be used instead of an ANCOVA.

4. Additional Exploratory Analysis

Pearson Correlations will be computed between PTSD+ participants' CAPS-5 scores and CSO participants' outcomes (all) [4]. This analysis will be conducted for baseline, midpoint (visit 9), primary endpoint (visit 16), 3-month follow-up (visit 17), and primary endpoint (visit 18). Correlations (r) and p values will be reported to assess the direction and magnitude of these relationships. This analysis is intended to explore the potential impact of CSO participants' responses to the given treatment on PTSD+ participants' CAPS-5 scores over time.

5. Process Measures

Long-term Follow-up Questionnaire (LTFU Questionnaire)
The LTFU Questionnaire nominal variables will be described in terms of frequencies and percentages, while ordinal and non-normal continuous variables will be described using sample mean, standard deviations, and range. Results will be reported for the total sample and by PTSD+ participants and CSO participants.

Reactions to Research Participation Questionnaire (RRPQ)
Frequency of responses will be tabulated for 'reasons for participation' for the total sample and by PTSD+ participants and CSO participants. Descriptive statistics will be computed for total scores for subscales and reported for the total sample and by PTSD+ participants and CSO participants.

6. Safety Analyses

The primary measure of safety will be reports of adverse events. Adverse events are Treatment Emergent Adverse Events (TEAE) defined as those AE's that occurred after dosing and existing medical history diagnoses that worsened during the study. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the MedDRA dictionary. For incidence reporting if a subject has more than one AE mapped to the same preferred term, that AE will be reported only once using the highest severity and closest relationship to study drug. Subject incidence of AEs will be displayed by group and by system organ class. AEs will also be summarized by severity. Subject incidence of SAEs will also be displayed. In addition to the listing of all AEs, a listing of SAEs and a listing of AEs leading to discontinuation of study drug will be included.

Summary tables of frequency listings of commonly reported AEs (Spontaneously Reported Reactions) mapped to preferred terms will be displayed during and after each experimental session by PTSD+ participants and CSO participants. Additional safety measures will be analyzed as follows:

Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and behavior will be summarized according to suggestions made in the Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide [5][5]. A positive response for suicidal ideation is counted when subjects respond "yes" to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS (i.e. a score > 0 for suicidal ideation score). Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when subjects answer "yes" to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS (i.e. a score > 0 for suicidal behavior score). The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated overall and by PTSD+ participants and CSO participants for each time period. Lifetime serious suicidal ideation and positive behavior frequencies will be compared to cumulative frequencies at all timepoints throughout the study.

Subjective Units of Distress (SUD) and Vital Signs

SUD scores will be calculated including frequencies and percentages in the total sample and by PTSD+ participants and CSO participants at experimental treatment 1 (visit 3) and experimental treatment 2 (visit 10). Vital signs include heart rate, body temperature, systolic and diastolic blood pressure, and will be summarized using descriptive statistics at baseline and at each post-baseline time point. Systolic and diastolic blood pressure, heart rate, and body temperature readings above the pre-determined cutoff will be reported using numbers and percentages by timepoint.

General Well-being

Therapists will assess PTSD+ participants' and CSO participants' general well-being using the General Well-being scale at each timepoint and on a daily basis for seven consecutive days after each experimental session. Frequencies, percentages, and mean (SD) total scores will be reported for the total sample and by PTSD+ participants' and CSO participants.

Adverse Events Requiring Medical Attention

All adverse events requiring medical attention will be collected from enrollment through the last follow-up. Each occurrence will be reported for the total sample and separately for PTSD+ participants and CSO participants.

Events Related to Medical History

Occurrences will be reported for the total sample and separately for PTSD+ participants and CSO participants.

- 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.

Timing of Analyses

The primary efficacy analysis will be conducted after all subjects complete the study. Subsequent analyses on this data set will not be conducted after initial analyses are performed, unless for further exploratory post-hoc analyses. Changes to protocol will not occur after primary analysis.

Statistical Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

References

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3. Hedges, L.V., *Distribution theory for Glass's estimator of effect size and related estimators*. J Educ Statistics 1981. **6**(2): p. 107-128.
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5. Nilsson, M.E., et al., *Columbia Suicide Severity Rating Scale Scoring and Data Analysis Guide*, in *CSSRS Scoring Version 2.0*. 2013: http://www.cssrs.columbia.edu/documents/ScoringandDataAnalysisGuide_Feb2013.pdf. p. 1-13.