MAPPUSX Statistical Analysis Plan

Version 1: 13 April 2021

SPONSOR	Multidisciplinary Association for Psychedelic Studies (MAPS) 1115 Mission Street Santa Cruz, CA 95060
SPONSOR REPRESENTATIVE	Rick Doblin, Ph.D. Executive Director, MAPS
SPONSOR DELEGATE & TRIAL ORGANIZER	Multidisciplinary Association for Psychedelic Studies (MAPS) 3141 Stevens Creek Blvd #40563 San Jose, CA 95117
SPONSOR DESIGNEE	Amy Emerson Chief Executive Officer MAPS Public Benefit Corporation
MEDICAL MONITOR(S)	Alia Lilienstein, M.D.
STATISTICIAN(S)	Scott Hamilton, Ph.D.
PREPARED BY	Scott Hamilton, Ph.D.
USE	In conjunction with relevant regulatory guidance

Table of Contents

List of Tables

List of Abbreviations

° C	Degrees Celsius
A:G	Albumin:Globulin
ACE	Adverse Childhood Experiences Questionnaire
ADHD	Attention Deficit/Hyperactivity Disorder
AE	Adverse Event
AED	Automatic External Defibrillator
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BDI-II	Beck Depression Inventory-II
BLS	Basic Life Support
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAPS-4	Clinician-Administered PTSD Scale for DSM-4
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
%CDT	%Carbohydrate-deficient Transferrin
CMC	Chemistry Manufacturing and Control
CPGS	Chronic Pain Grade Scale
CRA	Clinical Research Associate
C-SSRS	Columbia-Suicide Severity Rating Scale
DDIS	Dissociative Disorders Interview Schedule
DID	Dissociative Identity Disorder
dIGPP	Cohen's *d* Independent Groups Pre-test Post-test
DMF	Drug Master File
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSP-I	Dissociative Subtype of PTSD Interview
DUDIT	Drug Abuse Disorders Identification Test
EAT-26	Eating Attitudes Test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
ED	Emergency Department
EDC	Electronic Data Capture
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
ePRO	Electronic Participant Reported Outcome
EQ-5D-5L	EuroQol Five Dimensions – Five Levels Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIPAA	Health Insurance Portability and Accountability
HPA	Hypothalamic-pituitary-adrenal
HPMC	Hydroxypropyl Methylcellulose

HPQSF	Health and Work Performance Absenteeism and Presenteeism Short Form
IASC	Inventory of Altered Self-Capacities
IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IP	Investigational Product
IPF	Inventory of Psychosocial Functioning
IR	Independent Rater
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
kg	Kilogram
LEC-5	Life Events Checklist
LTFU	Long-term Follow-up
MAPS	Multidisciplinary Association for Psychedelic Studies
MAOI	Monoamine Oxidase Inhibitor
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
*m*ITT	Modified Intent-to-Treat
mmHg	Milligrams of Mercury
MMRM	Mixed Model Repeated Measure
MPBC	MAPS Public Benefit Corporation
ms	Millisecond
PCL-5	PTSD Checklist for DSM-5
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
RACT	Risk Assessment and Categorization Tool
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SCID-5-SPQ	SCID-5 Self-report Personality Questionnaire
SCS	Self-compassion Scale
SDS	Sheehan Disability Scale
SGOT	Serum Glutamic Oxaloacetic Transaminase
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SPGT	Serum Glutamic Pyruvic Transaminase
SRNU	Self-reported Nicotine Use
SSR	Sample size re-estimation
SSRI	Selective serotonin reuptake inhibitor
SUBJID	Subject Identifier
TAS-20	Toronto Alexithymia Scale
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid-stimulating Hormone

UFEC	Utilization of Facility-based and Emergent Care
U.S.	United States
VA	U.S. Department of Veterans Affairs
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization
WHO DDE	WHO Drug Dictionary Enhanced™

1.0 Definitions of Terms

Categorical data: refers to discrete (indivisible) variables, such as gender or ethnicity; data will be presented as total numbers of each category as needed to describe the sample

Completers: are defined as participants who complete all three planned experimental sessions and the PCL-5 outcome assessment atVisit 16.

Descriptive data: includes mean, median, standard deviation, minimum, and maximum of numerical data used as needed to describe the sample

Difference scores: consist of scores computed by subtracting one value from another, as subtracting Baseline from follow-up score, used to test for differences between and within groups to determine change as a function of experimental treatment over time

Dropouts: are defined as participants who withdraw consent due to any reason after dosing and no longer participate in the study, i.e. no further contact with investigators or site staff.

Efficacy: type of analysis used to assess therapeutic effects or benefits

Exploratory analyses: inferential or descriptive analysis of the data to determine trends that might lead to hypotheses for further study

Frequency listing: tabular listing of numbers and/or percentages of events used as needed to describe the sample or data characteristics

Outcome measures: primary and secondary study measures that are used to test the study hypotheses

Post-dosing Early Terminators: are defined as participants who discontinue study treatment but continue to participate in study evaluations and outcome assessments.

Pre-dosing Early Terminators: are defined as participants who discontinue participation after enrollment but before randomization during the Preparatory Period and never receive study drug.

Process measures: study measures or qualitative observations collected during the study that may increase depth of understanding of the condition and treatment, although not necessarily related to safety or efficacy

Protocol deviation: event that represents significant divergence from the intended study design as described in the protocol

Safety: assessment of indicators of potential risks and adverse events

Safety measures: study measures that assess safety of the Investigational Product (IP), such as heart rate monitoring, blood pressure, body temperature

Study design: all elements of a research project that define the study question, experimental methods, study procedures including blinding, measurement techniques, data workflow, and statistical analysis

Tabular listing: list of each variable or item for each individual participant either in total or by treatment group in a table format

2.0 Introduction

This document contains a Statistical Analysis Plan (SAP) for MAPPUSX "A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Therapy for the Treatment of Participants with Posttraumatic Stress Disorder."

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor to obtain marketing approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to therapy in patients with posttraumatic stress disorder (PTSD). Controlled Phase 1 studies, nonclinical studies, and investigator-initiated studies formed the basis for the Clinical Development Program of MDMA under Investigational New Drug (IND) #063384. MAPS-sponsored studies are implemented through MAPS' wholly owned subsidiary and delegate, the MAPS Public Benefit Corporation (MPBC).

This multi-site open-label safety extension study of manualized MDMA-assisted therapy for the treatment of participants with PTSD will be conducted in N≈100 participants, by invitation only.

The treatment consists of a flexible dose of MDMA, followed by a supplemental dose unless tolerability issues emerge administered with manualized therapy in three open-label approximately monthly Experimental Sessions. This Treatment Period is preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session is followed by threeIntegrative Sessions of non-drug therapy. Experimental Sessions are followed by an overnight stay; a sub-study will assess feasibility of Experimental Sessions without an overnight stay. The Primary Outcome measure, the change in PCL-5 (PTSD Checklist for DSM5) from Visit 3 is assessed at Visit 16. An independent Data Monitoring Committee (DMC) will review safety data as described in the DMC charter and at any time a Serious Adverse Reaction (SAR) occurs.

3.0 Study Objectives

3.1 Primary Objective

The primary objective of this study is to evaluate the effectiveness of MDMA-assisted therapy for PTSD, as measured by the reduction in PCL-5 total score from Visit 3 to Visit 16.

3.2 Secondary Objective

The key secondary objective of this study is to evaluate the effectiveness of MDMA-assisted therapy for PTSD in functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 to Visit 16.

3.3 Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of Adverse Events (AEs), Treatment Emergent AEs (TEAEs), AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behavior, and vital signs to support the package insert for MDMA-assisted therapy. The following safety objectives will evaluate the safety of MDMA-assisted therapy:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Medicinal Product (IMP) such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements
2. Assess incidence of AEs by severity
3. Assess incidence of TEAEs by severity
4. Assess incidence of TEAEs by severity reported during an Experimental Session, 1 day, and 2 days after IMP administration
5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function, suicidality, and abuse liability
6. Assess incidence of AEs by severity categorized as leading to discontinuation of IMP, resulting in death or hospitalization, and continuing at Study Termination
7. Assess incidence of SAEs
8. Assess incidence of concomitant medications taken during an Experimental Session, 1 day, and 2 days after IMP administration
9. Assess incidence of psychiatric concomitant medications taken during the Treatment Period
10. Assess incidence of positive or serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS)
11. Assess changes in blood pressure (BP), heart rate, and body temperature from pre-IMP administration to end of each Experimental Session

3.4 Exploratory Objectives

These objectives may be explored to characterize participants receiving MDMA-assisted therapy to support the primary objective:

1. Explore the effect of presence of secondary traumatic stressors identified on the Life Events Checklist (LEC-5) on the PCL-5 total severity analysis
2. Explore differences from Visit 3 to Visit 16 in:
    a. Depression (BDI-II)
    b. Chronic pain (CPGS)
    c. Quality of life (EQ-5D-5L)
    d. Nicotine use (SRNU)
    e. Eating habits (EAT-26)
    f. Workplace productivity (HPQSF)
3. Explore differences from Screening to Visit 16 in alcohol use (AUDIT) and drug use (DUDIT)

4.0 Measures

4.1 Primary Measure

- PCL-5 (PTSD Checklist)

4.2 Secondary Outcome Measure

- Sheehan Disability Scale (SDS)

4.3 Safety Measures

- Columbia Suicide Severity Rating Scale (C-SSRS)
- Adverse Events

- Treatment-emergent Adverse Events
- Serious Adverse Events
- Adverse Events of Special Interest
- Concomitant medication use
- Vitals signs during MDMA sessions

4.4 Exploratory Measures

- Life Events Checklist (LEC-5)
- Beck Depression Inventory II (BDI-II)
- Chronic Pain Grade Scale (CPGS)
- EuroQol Five Dimensions – Five Levels Questionnaire (EQ-5D-5L)
- Alcohol Use Disorders Identification Test (AUDIT)
- Drug Use Disorders Identification Test (DUDIT)
- Self-reported Nicotine Use (SRNU)
- EAT-26 (Eating Attitudes Test)
- HPQSF (Health and Work Performance Absenteeism and Presenteeism Short Form)
- Utilization of Facility-based and Emergent Care (UFEC)

5.0 Study Design

Table 1: Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 to 120 mg
2	80 or 120 mg	40 or 60 mg	80 to 180 mg
3	80 or 120 mg	40 or 60 mg	80 to 180 mg
		Total Cumulative Dose	240 to 480 mg

* Unless contraindicated

Table 2: Time and Events – Study Procedures

	Screening Period (1 to 6 weeks)			**Preparatory Period** (At least 5 days, depending on medication tapering)			
	Screening			**Preparatory**			
Visit	Phone Screening	Screening	IR Screening	V0	V1	V2	V3
Visit Description	Phone Calls	In-person Visits & Labs	Telemedicine	Enrollment	Prep. 1	Prep. 2	Prep. 3
Visit Timing	Prior to Initial Screening	Over 7 to 42 days	2 to 9 days after initial eligibility met	2 to 14 days post IR Screening	0 to 14 days after V0	At least 2 days after V1 (depending on tapering)	Post V2 & Taper, 1 to 14 days before V4
Initial Phone Screen	✓						
Informed Consent	Send Copy	✓					
Follow-up Phone Screen	✓						
Assess Eligibility	✓	✓	✓	✓	✓	✓	✓
Medical/Psychiatric History	✓ [A]	✓			✓	✓	✓
Past/Current Medication & Adherence	✓	✓		✓	✓	✓	✓
Weight		✓					
Resting Vitals		✓					
Physical Exam		✓					
ECG & Rhythm Strip		✓					
Clinical Lab Tests		✓					
Drug Screen		✓					✓
Pregnancy Screen		✓					✓
Enter Participant in eCRF		✓					
Independent Rater Assessment			✓				
Medication Taper				✓	✓	✓	
Study Enrollment				✓			
All AEs [B]				✓	✓	✓	✓
90-min Preparatory Session					✓	✓	✓
Phone Call Follow-up [C]						✓	
Measures (ePRO or Clinician-Administered [D]		✓	✓		✓	✓	✓

A At Screening, collect data on previous hospitalizations and healthcare utilization. Request participants to obtain medical/psychiatric records generated since the end of the parent study to bring to the in-person screening
[B] All Adverse Events (AEs) includes collecting Serious Adverse Events, AEs of Special Interest, AEs of Psychiatric Status, AEs requiring medical advice or attention, AEs that indicate withdrawal of a participant, and all other AEs
[C] If needed, call participant to confirm medication tapering and stabilization is complete prior to Visit 3
[D] Refer to Table 6: Time and Events-Measures for details

	Treatment Period 8 to 20 weeks												
	Treatment 1				**Treatment 2**				**Treatment 3**				**Study Termi-nation**
Visit	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Visit Description	Exp. 1	Int. 1.1	Int. 1.2 [F]	Int. 1.3 [F]	Exp. 2	Int. 2.1	Int. 2.2 [F]	Int. 2.3 [F]	Exp. 3	Int. 3.1	Int. 3.2 [F]	Int. 3.3 [F]	Study Termination
Visit Timing	1 to 14 days after V3	Morning after V4	10 to 18 days after V4	At least 2 days after V6; 1 to 14 days before V8	21 to 56 days after V4	Morning after V8	10 to 18 days after V8	At least 2 days after V10; 1 to 14 days before V12	21 to 56 days after V8	Morning after V12	10 to 18 days after V12	At least two days after V14	24 to 32 days after V12
Past/Current Medication & Adherence	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Drug Screen	✓				✓				✓				
Pregnancy Screen	✓				✓				✓				
All AEs [A]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Container Assignment [B]	✓				✓				✓				
Administer IMP	✓				✓				✓				
8-hour Exp. Session	✓				✓				✓				
BP, Pulse, Temperature	✓ [C]				✓ [C]				✓ [C]				✓ [D]
Potential Overnight Stay	✓				✓				✓				
90-min Integrative Session		✓	✓	✓		✓	✓	✓		✓	✓	✓	
Phone Call Follow-up [E]		✓				✓				✓			
Weight													✓
Blood Draw (CRP)													✓
Measures (ePRO or Clinician-Administered [G]	✓	✓ [E]	✓	✓	✓	✓ [E]	✓	✓	✓	✓ [E]	✓	✓	✓

[A] All Adverse Events (AEs) includes collecting Serious Adverse Events, AEs of Special Interest, AEs of Psychiatric Status, AEs requiring medical advice or attention, AEs that indicate withdrawal of a participant, and all other AEs
[B] Obtain container assignment 24 to 48 hours prior to each Experimental Session
[C] During Experimental Sessions, vitals are measured before Investigational Product administration, immediately before the supplemental dose is administered (or would be, if supplemental dose not given), and approximately 8 hours after initial dose, and as needed
[D] At Study Termination, only blood pressure needs to be measured
[E] 14 days of phone call follow-up: every other day after the Experimental Session; includes C-SSRS administration and AE collection
[F] All Integrative Sessions must be at least 2 days apart
[G] Refer to Table 6: Time and Events-Measures for details

		Screening		**Preparatory Period**			**Treatment 1**				**Treatment 2**				**Treatment 3**				**Study Termination**
	Visit #	Screening	IR Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Visit Description	**~Time to Complete Measure (minutes)**	Site Visit	Tele-medicine	Prep. Session 1	Prep. Session 2	Prep. Session 3	Exp. Session 1	Int. Sessions 1.1	Int. Session 1.2	Int. Session 1.3	Exp. Session 2	Int. Sessions 2.1	Int. Session 2.2	Int. Session 2.3	Exp. Session 3	Int. Sessions 3.1	Int. Session 3.2	Int. Session 3.3	Study Termi-nation
C-SSRS [A]	10	✓	✓			✓	✓[B]	✓	✓	✓	✓[B]	✓	✓	✓	✓[B]	✓	✓	✓	✓
MINI	75		✓																
LEC-5	5	✓				✓			✓				✓				✓		✓
PCL-5	8	✓				✓			✓				✓				✓		✓
SDS	2					✓													✓
BDI-II	5					✓													✓
CPGS	5					✓													✓
EQ-5D-5L	3					✓													✓
AUDIT	3	✓																	✓
DUDIT	3	✓																	✓
SRNU	3					✓													✓
EAT-26	6					✓													✓
HPQSF	5					✓													✓
UFEC	3	✓																	
~Total Time of Completing Measures (minutes)	**121**	**29**	**70**	**0** [C]	**0** [C]	**55**	**90**[B]	**10**	**23**	**10**	**90**[B]	**10**	**23**	**10**	**90**[B]	**10**	**23**	**10**	**58**

[A] All C-SSRS are Since Last Visit. The first assessment will measure suicidality since the last administration in the parent study. All subsequent administrations will assess suicidality since the last administration in this protocol.
[B] Conducted pre- and post-Investigational Product administration, and every other day for 14 days after Experimental Sessions.
[C] No planned measures to be assessed at Visit 1 or Visit 2

6.0 Randomization and Blinding

This is an open-label study with no randomization or blinding.

7.0 Sample Size and Power Considerations

This is a one-arm open-label study. Thus, no power nor sample size calculations are required.

8.0 Analyses

Every effort will be made to ensure complete, accurate and timely data collection and to avoid missing data, to ensure the completeness of the data which can impact the integrity and accuracy of the final study analysis. The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS® Version 9.4 or higher, and S-PLUS. In general, nominal variables will be described in terms of frequencies and percentages. Ordinal and non-normal continuous variables will be described using sample median and range.

Approximately normally distributed continuous variables will be described using sample mean and standard deviations and analyzed by parametric statistical tests. Otherwise, Wilcoxon rank-sum tests will be used. Categorical variable will be displayed by counts and percentages and analyzed by chi-squared tests. Except for the primary efficacy analysis, 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. If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001. 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. Selected results may be presented graphically using standard graphical software.

8.1 Analysis Sets

- *Safety*: all participants who receive any IP
- *All Enrolled*: all participants who signed informed consent

8.2 Missing Data Handling

All possible procedures within Good Clinical Practice (GCP) will be used to minimize Post-dosing Early Termination. All participants who receive IP in at least one Experimental Session will be included in all safety analyses.

8.2.1 Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for AEs 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.

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:
    a. The month and day of the first dose date will be imputed if the year matches the first dose date year.
    b. Otherwise, 'January' will be assigned.
3. If the day is unknown, then:
    a. The day of the first dose date will be imputed if the month and year match the first dose date month and year.
    b. Otherwise, the first day of the month will be assigned.

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 'December' will be assigned.
3. If the day is unknown, then the last day of the month will be assigned.

8.3 Protocol Deviations

Protocol deviations will be classified as major/minor by the MPBC protocol deviations review committee. The committee will determine the impact of the deviation on the study subjects' safety and rights, study compliance, data quality, and the proposed analyses. A subject level listing will report the description of the deviation and the impact.

A table of protocol deviations will summarize them by major/minor into the following categories:

- Informed Consent
- Inclusion/Exclusion
- Study Treatment
- Prohibited Concomitant Medication
- Trial Procedures
- Safety Reporting
- Discontinuation
- Miscellaneous

8.4 Baseline Values

Baseline values are from Baseline Visits for all measures, except C-SSRS, AUDIT, DUDIT, resting blood pressure (BP), Body Mass Index (BMI). For C-SSRS, the initial screening visit will be conducted with the 'Lifetime' version of the measure. The Independent Rater Screening assessment of 'Since Last Visit' suicidal ideation and behavior will be used as 'Baseline.' For the AUDIT and DUDIT measures and resting BP, BMI, results collected at Screening will be used as the Baseline value.

8.5 Participant Disposition and Dosing Summary

The Safety Set will be included in the summary of participant disposition and accountability summarized. The number and percent of participants who completed or discontinued the study will be displayed with reasons for early termination, where the percent is with respect to the total number of participants. The timepoint of doses and total MDMA (mg) administered will be summarized for the Safety Set.

8.6 Demographics and Baseline Characteristics

Participant demographic data and Baseline characteristics will be summarized descriptively.

8.7 Efficacy Analyses

For all primary, secondary, and exploratory endpoints descriptive statistics (n, mean, standard deviation, median, range, or counts and percentages where appropriate) will be provided. Longitudinal PCL-5 and SDS item scores will be plotted across visits to characterize the onset of treatment effect.

8.7.1 Primary Effectiveness Analysis

The primary analysis of the effectiveness of MDMA-assisted psychotherapy will be made using a Mixed Model Repeated Measure (MMRM) model to assess changes in PCL-5 scores throughout the study period from Baseline (Visit 3) through Visit 16. Baseline covariates (baseline PVL-5, age, gender, ethnicity, index trauma, complexity and severity of trauma, diagnosis of comorbid depression, diagnosis of comorbid Axis 2 diagnosis, adverse childhood experiences collected in the parent study) may be assessed for inclusion in the final model with an alpha level set at 0.05.

8.7.2 Secondary Effectiveness Analysis

The SDS will be analyzed in a similar manner to the primary analysis of the PCL-5.

8.7.3 Exploratory Analyses

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. In particular, MMRM models, linear regression, and/or ANCOVA models may be utilized to analyze the effect of MDMA in conjunction with psychotherapy on the following exploratory endpoints:

- Presence of secondary traumatic stressors identified on the Life Events Checklist (LEC-5) on the PCL-5 total severity analysis
- Depression (BDI-II)
- Chronic pain (CPGS)
- Quality of life (EQ-5D-5L)
- Nicotine use (SRNU)
- Eating habits (EAT-26)
- Workplace productivity (HPQSF)
- Alcohol use (AUDIT)
- Drug use (DUDIT)

These analyses will be clearly identified as exploratory in the final clinical study report.

8.8 Safety Analyses

Safety analyses will confirm safety data with summary tables listing exposure to IMP, unsolicited AEs, TEAEs, concomitant medications, suicidal ideation and behavior, and vital signs overall and by group. If a participant has more than one AE mapped to the same PT, that AE will be reported once using the highest severity. AEs that occur on Day 0 (Experimental Session), Day 1, Day 2

after IMP administration will be presented separately. Compare relative incidence of AEs during Experimental Sessions such as clinical signs and 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 of the IMP.

8.8.1 Analysis of Exposure

The total mg exposure of participants will be summarized. Data will be tabulated for the Safety Set.

8.8.2 Analysis of Adverse Events

The primary measure of safety will be the reporting of unsolicited AEs. All AEs collected from Enrollment to Termination will be categorized as follows:

- Pretreatment AEs are defined as AEs that occur during the Preparatory Period prior to the first dose in the first Experimental Session
- Treatment Emergent AEs are defined as AEs that occur during the Treatment Period from the first Experimental Session to the last Integrative Session
- AEs that occur on and two days after MDMA administration
- AESIs are defined as AEs specified in the protocol related to cardiac function and abuse liability
- Follow-up Period AEs are defined as AEs that occur during the Follow-up Period after the last Integrative Session through Termination
- AEs leading to discontinuation of IP
- AEs resulting in death or hospitalization.
- SAEs
- AEs continuing at Termination.

Verbatim terms on case report forms will be mapped to preferred terms (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 Frequency and incidence of AEs will be displayed by PT, sorted by SOC, severity, and seriousness. AEs will be analyzed and presented as follows:

- If a participant has more than one AE mapped to the same PT, that AE will be reported once using the highest severity
- Relationship will be determined by the Clinical Investigator
- AEs that occur on day of Experimental Sessions and two days after IP administration will be presented separately.

8.8.3 Concomitant Medications

Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized by treatment group, analysis set, and category. Concomitant medications taken on Day 0 (Experimental Session), Day 1, Day 2 after IMP administration will be presented separately. Any psychiatric concomitant medications will be tabulated by period (Preparatory, Treatment Period, Follow-up Period). Frequency and incidence of positive or serious ideation and suicidal behavior will be presented using descriptive statistics of C-SSRS scores in tabular format. Vital signs (heart rate, blood pressure, and body temperature) for Experimental Sessions will be summarized using descriptive statistics in tabular format listing values at pre-IMP administration, prior to the supplemental dose, and at the end of each Experimental Session.

8.8.4 Analysis of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be summarized according to suggestions made in the C-SSRS Scoring and Data Analysis Guide [1]. A positive response for suicidal ideation is counted when a participant answers "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). Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a participant answers "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). The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated by treatment group and time period (lifetime, screening, baseline, each Experimental Session (pre- and post-IP), Integrative Sessions, and endpoints). Frequency and incidence of positive or serious ideation and suicidal behavior will be presented using descriptive statistics in tabular format.

8.8.5 Summary of Vital Signs

Vital signs (heart rate, BP, and body temperature) for Experimental Sessions will be summarized using descriptive statistics in tabular format listing values at pre-IP, prior to the supplemental dose, and at the end of each Experimental Session. Change from Baseline in vital signs will be presented by study.

9.0 Timing of Analyses

Preliminary analyses and listing reviews will be ongoing throughout the studies to inform therapist supervision and assumptions made for other and ongoing trials. For clinical study reports and publications, only locked database files will be used. The final analysis will be conducted after all participants complete Visit 20 and the database is locked.

References

1. 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.