MP18 Statistical Analysis Plan

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USE	In conjunction with relevant FDA, EMA guidance

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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
EEA	European Economic Area
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
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
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 two planned experimental sessions and the CAPS-5 outcome assessment 14 weeks after enrollment (Visit 14).

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.

Effectiveness: 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 effectiveness

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 enrollment, 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 an open-label study (MP18), "An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects with Posttraumatic Stress Disorder." A separate SAP for the Optional fMRI Sub-Study is to be prepared.

This study is similar in study design, objectives, and protocols to MP16 and MP17, which are open-label three-session studies. The differences are the number of sessions (2 sessions in MP18, 3 sessions in MP16 and MP17), the number of subjects enrolled in each study, location of sites (MP18 at EU sites, MP16 at USA and MP17 at Canada sites) and the source and dose of MDMA. MDMA used in all studies have similar purity and drug properties. MP18 tests a flexible dosing regimen of 80mg MDMA in Session 1, and 80mg or 120mg MDMA in Sessions 2, each followed by a supplemental half-dose. MP16 tests a flexible dosing regimen of 80 mg MDMA in Session 1, and 80 mg or 120 mg MDMA in Sessions 2 and 3, each followed by a supplemental half-dose. MP17 tests a flexible dosing regimen of 100mg MDMA in Session 1, and 100mg or 120mg MDMA in Sessions 2 and 3, each followed by a supplemental half-dose.

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA) in conjunction with psychotherapy in persons with posttraumatic stress disorder (PTSD). MAPS Europe B.V. has delegated statistical analysis to MAPS Public Benefit Corporation (MPBC).

The open-label Phase 2 MP18 study will serve as the lead-in to the sponsor's planned Phase 3 study in the European Economic Area (EEA). Only sites planned for Phase 3 will participate in these studies. These open-label lead-in Phase 2 studies will serve to validate assumptions made for statistical power calculations supporting planned Phase 3 clinical trials and will provide crosscultural verification data on the updated version of the instrument for the Primary Outcome measure, the Clinician Administered PTSD Scale for DSM-5 (CAPS-5), which will be used in Phase 3. In addition, these studies will gather supportive data on the safety and effect of manualized MDMA-assisted psychotherapy while providing an opportunity for clinical supervision to planned Phase 3 therapy teams. These studies will explore reproducibility of findings in a multi-site format to confirm the Phase 3 study design in the EEA region.

3.0 Study Objectives

3.1 Primary Objective

The primary objective of this study is to evaluate the effectiveness of MDMA-assisted psychotherapy for treatment of PTSD, as measured by the estimand of change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

3.2 Secondary Objective

The secondary objective is to evaluate the effectiveness of MDMA-assisted psychotherapy for PTSD in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline).

3.3 Safety Objectives

The overall safety objective is to assess severity, incidence and frequency of AEs, 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 psychotherapy. The following safety objectives will evaluate the safety of MDMA-assisted psychotherapy:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Product (IP), 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 Treatment Emergent AEs (TEAEs) by severity.
4. Assess incidence of TEAEs by severity taken during an Experimental Session and through 2 days after IP administration.
5. Assess incidence of AESIs, defined as AEs specified inthe protocol related to cardiac function and abuse liability.
6. Assess incidence of AEs by severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination.
7. Assess incidence of SAEs.
8. Assessincidence of psychiatric concomitant medications taken during an Experimental Session and through 2 days after IP administration.
9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.
10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).
11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IP administration to end of each Experimental Session.

3.4 Exploratory Objectives

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

1. Explore the effect of presence of secondary traumatic stressors (LEC-5) on the CAPS-5 Total Severity analyses
2. Explore changes within-participants in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal, as measured by changes in CAPS-5 subscale scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline)
3. Explore the effect of adverse childhood experiences (ACE) on the CAPS-5 Total Severity analyses
4. Explore changes in:
    - Dissociative symptoms associated with PTSD (DSP-I)
    - Depression (BDI-II)
    - Chronic pain (CPGS)
    - Quality of life (EQ-5D-5L)
    - Self-compassion (SCS)
    - Addictive behaviors including: alcohol use (AUDIT), drug use (DUDIT), and nicotine use (SRNU)
    - Eating habits (EAT-26)

- Healthcare utilization (UFEC) and economic productivity
- Subjective effects (SE)

4.0 Measures

4.1 Primary Measure

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

4.2 Secondary Outcome Measure

- Sheehan Disability Scale (SDS)

4.3 Safety Measures

- Treatment-emergent Adverse events
- Concomitant medication use
- Vitals signs during MDMA sessions
- Columbia Suicide Severity Rating Scale (C-SSRS)

4.4 Exploratory Measures

- Life Events Checklist (LEC-5)
- Adverse Childhood Experience Questionnaire (ACE)
- Dissociative symptoms associated with PTSD (DSP-I)
- Depression (BDI-II)
- Chronic pain (CPGS)
- Quality of life (EQ-5D-5L)
- Self-compassion (SCS)
- Addictive behaviors including: alcohol use (AUDIT), drug use (DUDIT), and nicotine use (SRNU)
- Eating habits (EAT-26)
- Healthcare utilization (UFEC)
- Subjective effects (SE)

5.0 Study Design

Table 1: Dose Regimen of MDMA

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 milligrams (mg)	40 mg	80 mg to 120 mg
2	80 or 120* mg	40 or 60 mg	80 mg to 180 mg
		Total Cumulative Dose	160 mg to 300 mg

* Unless contraindicated

Table 2: Time and Events – Study Procedures

	Screening Period (2 to 6 weeks)				**Preparatory Period w/ Enrollment Confirmation** (2 to 11 weeks)			
	Screening			**Enrollment**	**Preparatory**		**Baseline CAPS-5 T1**	**Baseline & Enrollment Confirmation**
Visit	Phone Screening	Screening	IR Screening	V0	V1	V2	V3	V4
Visit Description	Phone Calls	In-person Visits & Labs	Tele-assessment	Enrollment	Prep. 1	Prep. 2	Tele-assessment	Prep. 3 & Enrollment Confirmation
Visit Timing	Prior to Initial Screening	Over 3 weeks (-2 /+1 weeks)	2 days after initial eligibility met (+7 days)	2 days post IR Screening (+12 days)	Within 1 week of V0 (0 to 12 days)	2 to 21 days of V1	Post V2 & Taper	3 to 6 days after V3; 1 to 4 days before V5
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 [B]		✓						
Record			✓		✓	✓	✓	✓
Medication Taper				✓	✓	✓		
Study Enrollment				✓				✓ Confirmed
All AEs [C]				✓	✓	✓		✓
90-min Preparatory Session					✓	✓		✓
Phone Call Follow-up [D]						✓		

[A] At Screening, collect data on previous hospitalizations, healthcare utilization and economic productivity. Request participants to obtain medical/psychiatric records to bring to the in-person screening.

[B] Participants will be entered into the eCRF after the IR visit is scheduled

[C] 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

[D] If needed, call participant to confirm medication tapering and stabilization is complete prior to Visit 3

	Treatment Period ~8 weeks (+/-3 weeks)									**Follow-up Period & Study Termination** (~4 weeks) 13 weeks (+/-3 weeks) post baseline	
	Treatment 1					**Treatment 2**				**Primary Outcome**	**Study Termination**
Visit	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Visit Description	Exp. 1	Int. 1.1	Int. 1.2	CAPS-5 T2: Tele-assessment	Int. 1.3	Exp. 2	Int. 2.1	Int. 2.2	Int. 2.3	CAPS-5 T3 Outcome: Tele-assessment [I]	Study Termination
Visit Timing	Within 1 week of V3	Morning after V5	3 to 14 days after V5	18 to 30 days after V5	20 to 34 days after V5	21 to 35 days after V5	Morning after V10	3 to 14 days after V10	20 to 34 days after V10	13 weeks post V5 (+/-3 weeks)	2 days post V14 (-1/+7 days)
Past/Current Medication & Adherence	✓	✓	✓		✓	✓	✓	✓	✓		✓
Drug Screen	✓					✓					
Pregnancy Screen	✓					✓					
Record	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
All AEs [E]	✓	✓	✓		✓	✓	✓	✓	✓		✓
Administer IP	✓					✓					
8-hour Exp. Session	✓					✓					
BP, Pulse, Temperature [F]	✓					✓					✓ [G]
Overnight Stay	✓					✓					
90-min Integrative Session		✓	✓		✓		✓	✓	✓		
Phone Call Follow-up [H]		✓					✓				
Weight											✓

[E] 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

[F] 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

[G] At Study Termination, only blood pressure needs to be measured

[H] 4 days of phone call follow-up: Day 2 and 7 after the Experimental Session, with two additional calls in between

[I] All visits must be scheduled to ensure that the Primary Outcome CAPS-5 T3 assessment is within the overall window provided: 13 weeks (+/-3 weeks) post V5

Table 3: Time and Events – Study Measures

		Screening		Baseline & Enrollment Confirmation		Treatment 1				Treatment 2			Follow-up & Study Termination	
	Visit #	Site [A]	IR Screening	IR V3	V4	V5	V6&7	IR V8	V9	V10	V11&12	V13	IR V14	V15
Visit Description	**~Time to Complete Measure (minutes)**	Site Visit	Tele-assessment	Tele-assessment	Site Visit	Exp. Session 1	Int. Sessions 1.1 & 1.2	CAPS-5 T2: Tele-assessment	Int. Session 1.3	Exp. Session 2	Int. Sessions 2.1 & 2.2	Int. Session 2.3	CAPS-5 T3: Outcome: Tele-assessment	Study Termi-nation
CAPS-5	90 (Baseline) 60 (all others)			✓				✓					✓	
SDS	2			✓				✓					✓	
DSP-I	15			✓				✓					✓	
C-SSRS [B]	10	✓	✓		✓	✓[C]	✓		✓	✓[C]	✓	✓		✓
MINI	15		✓											
CIPD-SR	20	✓												
CIPD	60		✓											
LEC-5	5	✓			✓				✓			✓		✓
PCL-5	8	✓			✓				✓			✓		✓
DDIS [D]	5		✓											
ACE	4				✓									
BDI-II	10 (Baseline) 5 (all others)				✓									✓
CPGS	5				✓									✓
EQ-5D-5L	3				✓									✓
SCS	6				✓									✓
AUDIT	3	✓												✓
DUDIT	3	✓												✓
SRNU	3				✓									✓
EAT-26	6				✓									✓
UFEC	3				✓									
SE	2					✓				✓				
~Total Time of Completing Measures (minutes)		**49**	**105**	**107**	**50**	**12**	**10**	**77**	**23**	**12**	**10**	**23**	**77**	**57**

[A] Ensure that LEC-5 and CIPD-SR results are sent to the Independent Rater
[B] First C-SSRS is a Lifetime assessment, other assessments are Since Last Visit
[C] Conducted pre- and post-IP administration, and at phone calls on Days 2 and 7 after Experimental Session
[D] The relevant questions (117 to 132) from the DDIS will be asked by the Independent Rater during the IR Screening visit. The entire measure will never be administered.

6.0 Randomization and Blinding

MP18 is an open-label study with no randomization or blinding of treatment.

7.0 Sample Size and Power Considerations

MP18 is a one-arm interventional study. Thus, no power nor sample size calculations were 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 normal variables will be described using sample mean and standard deviations and analyzed by parametric statistical tests. Except for the primary effectiveness 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
- *Modified Intent-To-Treat (mITT):* all enrolled participants who receive IP in at least one blinded Experimental Session (Visit 5) and have at least one follow-up CAPS-5 assessment post-treatment
- *Per Protocol (PP):* all randomized participants who meet eligibility criteria, who receive IP in two Experimental Sessions, and have two follow-up CAPS-5 assessments post-treatment
- *Not Per Protocol (NPP):* all participants who are included in the mITT set but not the PP set

8.2 Missing Data Handling

All possible procedures within Good Clinical Practice (GCP) will be used to minimize Post-dosing Early Termination. Based on the US Phase 2 data it is expected that up to 5% of enrolled

and randomized participants will terminate early. Post-dosing Early Terminators will be compared to the Completers using baseline demographics and CAPS-5 Total Severity Score at baseline. Participants who are removed from the study after they are enrolled and receive IP but do not complete the study may fall into one of these categories: Post-Dosing Early Termination or Dropout. If the participant has received IP in at least one Experimental Session and completed one CAPS-5 assessment beyond Baseline, they will be considered evaluable. All participants who receive IP in at least one Experimental Session will be included in all safety analyses. Post-Dosing Early Termination are participants who discontinue study treatment but continue to participate in study evaluations and outcome assessments. Data collection by IRs will continue on the same schedule as planned through Study Termination visit procedures. Dropouts are defined as a participant who decides to withdraw consent. They will terminate without further follow-up. If the participant agrees, they will complete a final CAPS-5 assessment and Study Termination visit procedures. These participants are defined as dropouts who withdraw consent due to any reason after receiving at least one dose of IP and no longer participate in the study, i.e. no further contact with investigators or site staff. Data collected on study participants up to the time of withdrawal of consent will remain in the trial database in order to maintain scientific validity. All observed CAPS-5 data up to the point of discontinuation of treatment will be included in the MMRM model of the *de jure* estimand from Post-dosing Early Terminators. Participants will not be replaced. All observed CAPS-5 data from Post-dosing Early Terminators and Dropouts collected prior to and after early termination will be included in the supportive effectiveness analysis of the *de facto* estimand.

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

A major deviation will be defined as participants enrolled but did not meet eligibility criteria during the course of the study, or any deviations that affect safety or overall data integrity, particularly if it relates to study endpoints. The number of participants in each protocol deviation

category listed below will be summarized by analysis set. Individual participants will appear in a listing.

Possible protocol deviations include the following categories:

- Participant entered study but did not meet criteria
- Participant developed withdrawal criteria but was not withdrawn
- Participant received excluded concomitant treatment
- Protocol procedure not performed per protocol
- Participant received incorrect treatment or incorrect dose
- Protocol procedure performed out of range
- 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 overall. 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. The demographic data and baseline characteristics will be summarized for the Safety Set and overall.

8.7 Effectiveness 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 overall. Longitudinal CAPS-5 Total Severity Score and SDS item scores will be plotted across visits to characterize the onset of treatment effect.

8.7.1 Primary Effectiveness Analyses

The *de jure* estimand of treatment effectiveness will be used to estimate the change in CAPS-5 score from baseline due to MDMA-assisted psychotherapy on PTSD symptom severity in the intended population of patients with PTSD from any cause. The primary estimator of effectiveness will be the mean change in CAPS-5 Total Severity Scores from Baseline to 14 weeks after start of dosing (Visit 14). Least squares means from a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) will be used to estimate the change

in CAPS-5 from baseline to each visit. CAPS-5 data collected after treatment discontinuation will not be included in the *de jure* estimand. Missing data will not be imputed.

8.7.2 Key Secondary Effectiveness Analyses

For the key secondary analysis of effectiveness, the *de jure* estimand will be used to estimate the change from baseline due to MDMA-assisted psychotherapy on PTSD on the SDS in the intended population of patients with PTSD from any cause. The SDS is a 3-item scale measuring the severity of disability in the domains of work, family life/home responsibilities and social/leisure activities. Each of these three domains is scored on a ten-point Likert scale, where a score of 0 is 'not at all impaired', 5 is 'moderately impaired' and 10 is 'very severely impaired'. For each study participant at each visit, the responses on the 3 items of the SDS will be summarized with a mean. In cases where the response on item 1 is not applicable, it will not be considered missing data. Thus, missing data assumptions and methodologies are not required when item 1 is not answered. Whereas when all 3 items have a response, the summary measure is the mean of the 3 item responses, in the cases where item 1 is not answered the summary measure will consist of the mean of items 2 and 3. It is expected that no more than 20% participants will have not have an applicable score for item 1, based on prior studies of paroxetine with PTSD. To limit missing data and ensure standardized administration, the SDS will be administered in a clinician-rated format during the same visits as the CAPS-5 by the centralized Independent Rater Pool.

A secondary estimator of effectiveness will be the mean change in SDS Mean Scores from Baseline to 14 weeks after start of dosing (Visit 14). Least squares means from a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) will be used to estimate the change from baseline to each visit. SDS data collected after treatment discontinuation will not be included in the *de jure* estimand. Missing data will not be imputed and will be considered missing at random.

8.7.3 Exploratory Analyses

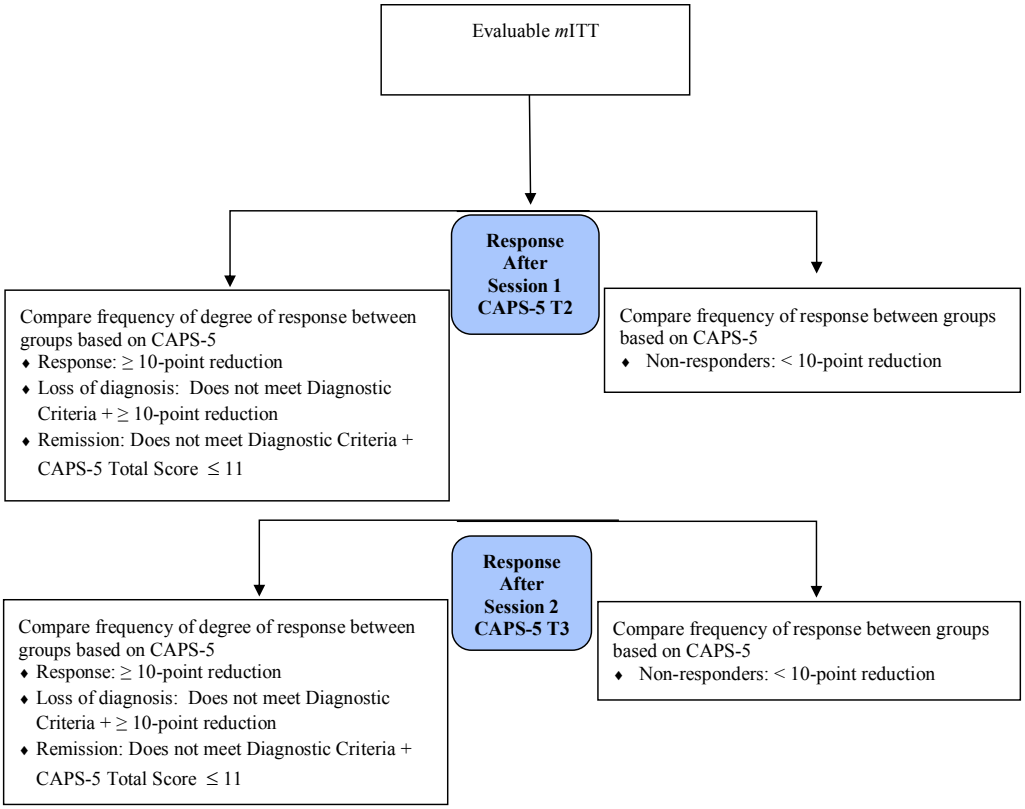
Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified as such in the final clinical study report or in the clinical study report addendum.

In exploratory analyses, additional baseline covariates (age, gender, ethnicity, index trauma, complexity and severity of trauma, medication tapering, diagnosis of comorbid depression, diagnosis of comorbid Axis 2 diagnosis, adverse childhood experiences) may be assessed for inclusion in the model at a $p<0.05$. One-group pretest-posttest Cohen's *d* effect size will be estimated.

8.7.4 Responder Analyses

The CAPS-5 produces a Total Severity Score based on severity of PTSD symptom domains described in the DSM-5, as well as a categorical rating indicating whether a participant meets PTSD diagnostic criteria. A psychometric validation study found the following severity score ranges for the CAPS-5: Asymptomatic (0-10), Mild (11-22), Moderate (23-34), Severe (35-46), Extreme (47+). Based on these data, a 10-point reduction in CAPS-5 Total Severity Score is clinically meaningful. As an alternate definition of treatment response to assess clinical significance of study outcomes, the sponsor will conduct a responder analysis to support findings from the primary effectiveness analysis, and to explore how many single-dose treatments are needed to achieve response (See Figure 1).

Figure 1: CONSORT for PTSD Responder Analysis After Treatment



[1] Response at T2, and T3 will be in comparison to Baseline at T1.

8.8 Safety Analyses

Safety assessment analyses for this study will include summaries of unsolicited adverse events, concomitant medications, suicidal ideation and behavior, and vital signs. Qualitative safety analyses will examine safety data with summary tables listing drug exposure, concomitant medications/therapies, unsolicited AEs, and percentages tabulated overall.

8.8.1 Analysis of Exposure

The frequencies and percentages of participants with exposure 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 or placebo 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 20.0 (Hierarchy), WHO DRUG Enhanced Mar-2018 B3 (Hierarchy and Ingredients).

Frequency and incidence of AEs will be displayed by PT, sorted by SOC, and summarized by treatment group, analysis set, category (as defined above), 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 based on relative incidence of TEAEs with at least two-fold difference between MDMA vs. placebo
- 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 investigational product
- AEs that occur on day of Experimental Sessions and two days after IP administration will be presented separately.

8.8.3 Concomitant Medications

A secondary measure of safety will be the reporting of concomitant medications. All concomitant medications collected from Screening to Study Termination will be categorized as follows:

- Pretreatment medications are defined as medications taken prior to and after signing informed consent and those taken during the Preparatory Period prior to the first Experimental Session. A stop date is expected prior to the first Experimental Session for any medications requiring a change in dose, a skipped dose, or tapering.
- Treatment Period concomitant medications are defined as those taken or continued during the Treatment Period from the first Experimental Session to the last Integrative Session. A stop date is expected prior to the each Experimental Session for any medications requiring a change in dose, a skipped dose, or tapering.
- Concomitant medications with a start date of the day of and two days after IP administration

- Follow-up Period concomitant medications are defined as those taken or continued during the Follow-up Period after the last Integrative Session through Termination
- Any concomitant medications that are tapered
- Any concomitant medications that are taken to treat an AE
- Any concomitant medications that are taken to treat an SAE
- Any excluded concomitant medications taken as a deviation from the protocol.

Concomitant medications on case report forms will be classified using the WHO Drug Dictionary Enhanced™ (WHO DDE). Frequency and incidence of concomitant medications will be displayed by generic name, sorted by class, and summarized by treatment group, analysis set, and category as defined above. Concomitant medications will be analyzed and presented as follows:

- Concomitant medications taken on the day of and two days after IP administration will be presented separately
- Any psychiatric concomitant medications by period.

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.

9.0 Timing of Analyses

Preliminary analyses and listing reviews will be ongoing throughout the study to inform therapist supervision and assumptions made for the upcoming Phase 3 trial. For clinical study reports and publications, only locked database files will be used. The primary effectiveness analysis will be conducted after all participants complete Visit 15 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.