MP-12 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 Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Subjects with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
LATEST PROTOCOL	Amendment 6 Version 1, April 30, 2015
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Table of Contents

1.0 List of Abbreviations

AE(s)	Adverse Event(s)
ANOVA	Analysis of Variance
BDI-II	Beck Depression Inventory-II
BP	Blood Pressure
BT	Body Temperature
CAPS-4	Clinician Administered PTSD Scale-4
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DES-II	Dissociative Experiences Scale-II
ES	Effect Size
GAF	Global Assessment of Functioning
GWB	General Well-being
HR	Heart Rate
mITT	Intent To Treat
MAPS	Multidisciplinary Association for Psychedelic Studies
MDMA	3,4-methylenedioxymethamphetamine
MPBC	MAPS Public Benefit Corporation
PASAT	Paced Auditory Serial Addition Test
PDS	PTSD Diagnostic Scale
PP	Per Protocol
PTSD	Posttraumatic Stress Disorder
PSQI	Pittsburgh Sleep Quality Index
PTGI	Post Traumatic Growth Inventory
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized Controlled Trial
RRPQ	Reactions to Research Participation Questionnaire
SBP	Systolic Blood Pressure
SOCQ	States of Consciousness Questionnaire
SUD	Subjective Units of Distress

2.0 Introduction

This document presents a Statistical Analysis Plan (SAP) for MAPS study protocol MP-12, a Phase 2 pilot clinical trial designed to evaluate the safety and efficacy of MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD.

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 unblinded or inferential or descriptive analyses of data pertaining to the MAPS MP-12 study. SAS programming may occur as study data accumulate in order to have analysis programs ready at the time of unblinding of the clinical team. In such an event, arbitrary treatment group assignments must be randomly linked to subjects, effectively rendering any output of programs meaningless. For the reasons stated here the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

3.0 Background

This Phase 2 pilot study will examine the safety and efficacy of manualized MDMA-assisted psychotherapy in subjects with chronic, treatment-resistant PTSD of at least six months duration who were unable to achieve remission despite having received prior treatment with either pharmacotherapy or psychotherapy of adequate dose/duration or who discontinued treatment due to lack of tolerability. Two active doses of MDMA (125mg and 100mg) and a comparator dose (40mg) will be assessed in Stage 1, as will the benefit of three versus two active dose sessions. Subjects who received the 100mg dose in their first two Stage 1 experimental sessions will be given the option to titrate up to 125mg in their third Stage 1 experimental session. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over and take part in a second study segment, referred to as Stage 2, with three open-label experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Two types of co-therapist teams will conduct the study. Each team will have an experienced therapist with a background consistent with that required in the treatment manual paired with either another experienced therapist or an “intern” co-therapist that is either pre-licensure, is licensed but with less experience, has a different therapy background than indicated in the manual, or practices a different healing profession (physician, nurse, social worker).

This study is designed to obtain estimates of effect size for safety and efficacy. The data will be combined with ongoing Phase 2 dose response studies in a meta-analysis. Cognitive function will also be assessed at baseline, one month after the second experimental session and two months after the third experimental session with active dose MDMA. This study is also intended to continue the development of a manualized psychotherapeutic approach to this potential treatment.

4.0 Study Objectives

4.1 Primary Objective

- Assess changes in PTSD symptoms in each active dose group and the comparator dose group, as measured by last-month Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

4.2 Secondary Objectives

The following objectives will compare each active dose group and the comparator dose group in Stage 1:

- Assess changes in self-reported PTSD symptoms as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory-II (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functionality (GAF) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociative Experiences Scale II (DES-II) at baseline and the primary endpoint.
- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) at baseline and the primary endpoint.

The following objectives will compare effects in specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, and global function, sleep quality, dissociation symptoms via CAPS and PDS, BDI-II, GAF, PSQI, PTGI (in reference to start of the study), and DES-II one year after the final experimental session for each subject.

The following objectives will include exploratory analyses intended to inform future protocol design:

- Explore the effects of each experimental session upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Assess the effect of the third experimental session for active dose subjects in Stage 1 and Stage 2 using CAPS, PDS, BDI-II, GAF, PSQI, PTGI (in reference to start of the study), and DES-II.
- Assess the ability of the investigators and subjects to accurately guess treatment group assignment in Stage 1.
- Correlate adherence to the treatment manual with Global CAPS scores using adherence criteria ratings to assess videos of psychotherapy sessions.

4.3 Safety Objectives

The safety objectives of the study are to monitor and assure safety of subjects during and after the experimental sessions by assessing physiological effects, psychological distress, adverse events, spontaneously reported reactions and suicidality.

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during some visits prior to experimental sessions, twice during experimental sessions, and several times after each experimental session, with comparisons made between subjects in each treatment group.
- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by treatment group, and end of Stage 1/end of Stage 2 for maximal exposure.
- Subjective Units of Distress (SUD) and vital signs including blood pressure, heart rate, and temperature will be measured during each experimental session, and vital signs will be compared between subjects in each treatment group.
- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.
- Serious adverse events, adverse events, and spontaneously reported reactions will be collected during the study, as described in Section 8.5 of the protocol.

5.0 Study 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 randomized, double-blind, dose response pilot study will examine the safety and efficacy of MDMA-assisted psychotherapy in subjects diagnosed with chronic, treatment-resistant PTSD of at least six months duration. Stage 1 will include two blinded and one open-label MDMA-assisted psychotherapy session scheduled approximately one month apart with a male/female co-therapist team. There will also be a moderate course of preparatory and integrative psychotherapy sessions as described in the Time and Events Table.

Upon enrollment, subjects will be randomly assigned to receive either active dose 1 (12 subjects), active dose 2 of MDMA (nine subjects), or comparator dose (five subjects). In Stage 1, subjects will meet with their therapist team for three preparatory sessions and two blinded experimental psychotherapy sessions of MDMA-assisted psychotherapy. One month after the second experimental session, the primary endpoint assessment will take place, after which the blind will be broken. Subjects who receive one of the active doses will receive a third open-label experimental session with similar procedures. Subjects who receive the active dose 2 during the first two experimental sessions will be given the option to increase their dose in the third experimental session to match the active dose 1 treatment group. Subjects who receive the comparator dose will be offered the option to continue to the open-label Stage 2 unless they meet any exclusion criteria for study participation. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. After a single preparatory

session, active dose 2 will be administered at the first session and the therapists will choose one of the two active doses of MDMA for the second and third experimental sessions, with an optional supplemental half dose at each of three experimental sessions at time points equivalent to those in Stage 1 (See Time and Events Table).

PTSD symptoms will be assessed throughout Stage 1. For subjects continuing on to Stage 2, PTSD symptoms will be assessed throughout Stage 2. All subjects will complete a follow-up occurring two months after their last experimental session in Stage 1 and Stage 2, if applicable. In addition all subjects will complete a visit 12 months after their final experimental session where outcome measures and a questionnaire on any lasting benefits or harms of the treatment will be administered (see Time and Events Table).

Table 4.0-1: Dose Regimen

Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose	Min-Max Cumulative Dose with Titration
Active Dose 1	125 mg	62.5 mg	125-187.5 mg	N/A
Active Dose 2	100 mg	50 mg	100-150 mg	N/A
Active Dose 2	100 mg	50 mg	100-150 mg	N/A
+ Optional Titration Dose	+25 mg	+12.5 mg	N/A	125-187.5 mg
Comparator Dose	40 mg	20 mg	40-60 mg	N/A

Table 2. Time & Events Stage 1	**Screen/ Baseline**	**Preparatory Sessions**	**Experimental Session 1**		**Experimental Session 2**		**Primary Endpoint**	**Experimental Session 3**		**End of Stage 1**
Visit #	Prior to enrollment	V1,2,3	V4	V5,6,7	V8	V9,10,11	V12	V13 [N]	V14,15,16 [N]	V17[N]
Type of Visit	Screening	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Experimental	Integrative	Outcome
Visit Timing	Over 2 mo. prior to V1	Appr.1 week apart	3-5 weeks post baseline	Between V4 and V8	3-5 weeks post V4	Between V8 and V12	1 month post V8	After V12	Between V13 and V17	2 months post V13
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Physical Exam, ECG	✓									
Brief Neurological Exam	✓									
SCID	✓									
Clinical Lab Tests, w/ HIV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication Taper (if applicable)		✓								
Study Enrollment if eligible		✓[O]								
Record to Audio/Video		✓	✓	✓	✓	✓		✓	✓	
General Well-Being		✓	✓	✓	✓	✓	✓	✓	✓	
Drug Screen	✓		✓		✓			✓		
Pregnancy Screen (if applicable)	✓		✓		✓			✓		
Obtain container assignment			✓[B]		✓[B]					
CAPS, GAF, BDI-II, PSQI, PTGI, DES-II	✓						✓[L]			✓
RBANS/PASAT	✓						✓			✓
PDS	✓			✓[M]			✓		✓[M]	✓
C-SSRS	✓	✓[G]	✓[C,D,E]	✓[I]	✓[C,D,E]	✓[I]	✓	✓[C,D,E]	✓[I]	✓
Administer Drug + Therapy			✓		✓			✓		
Monitoring of BP, Pulse, and Temp.			✓		✓			✓		
SUD			✓[E,F]		✓[E,F]			✓[E,F]		
Belief of Condition Assignment				✓[K]		✓[K]				
Overnight Stay, SOCQ			✓		✓			✓		
Integrative Therapy Session				✓[A]		✓[A]			✓[A]	
Seven Days Telephone Contact				✓		✓			✓	
AEs Requiring Medical Attention		✓	✓	✓	✓	✓	✓	✓	✓	✓
Spont. Reported Reactions & all AEs			✓[J]	✓	✓[J]	✓	✓	✓[J]	✓	
Changes in Tinnitus and/or Pain	✓[P]		✓[E,P]	✓[E,P]	✓[E,P]	✓[E,P]	✓[P]	✓[E,P]	✓[E,P]	✓[P]
AEs of psychiatric status or withdrawal		✓	✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓

Issue Memory Aid Card										✓[H]
Unblinding							✓			
Perception of Experimental Sessions							✓[N]			✓[N]
RRPQ										✓[H]

A = First Integrative session is one day after experimental session; B = At least 24 hours prior to experimental session; C = Approximately six hours post MDMA; D = At the beginning of the session; E = As needed; F = Approximately every 60 minutes; G = Given on 2nd preparatory session after washout; H = Only for subjects starting long-term follow-up; I = All visits and Day 2 and Day 7 phone calls only; J = Reactions collected for seven days post experimental session; K = On the day of the first integrative session following the experimental session; L = One month after the second experimental session but before the third experimental session; M = On the day of the third integrative session; N = Active dose subjects only; O = Only on Visit 1; P = Only in subjects with pre-existing tinnitus and/or chronic pain.

Time of Events Stage 2	**Preparatory Session**	**Experimental Session 1**		**Experimental Session 2**		**Secondary Endpoint**	**Experimental Session 3**		**End of Stage 2**	**Long-term Follow-up**
Visit #	V18*	V19	V20,21,22	V23	V24,25,26	V27	V28	V29, 30, 31	V32	LTFU
Type of Visit	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Experimental	Integrative	Outcome	Follow-up
Visit Timing	Within 1 month post V12*	1 week post V18	Between V19 and V23	3-5 weeks post V19	Between V23 and V27	1 month post V23	1 month post V23	Between V28 and V32	2 months post V28	1 year post V13 or V28
Confirm Informed Consent	✓									
Confirm Inclusion/Exclusion	✓									
Enrollment in Stage 2	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Record to Audio/Video	✓	✓	✓	✓	✓		✓	✓		
General Well-Being	✓	✓	✓	✓	✓	✓	✓	✓		
Drug Screen		✓		✓			✓			
Pregnancy Screen (if applicable)		✓		✓			✓			
CAPS, GAF, BDI-II, PSQ, PTGI, DES-II	Use V12*					✓[H]			✓	✓
RBANS/PASAT									✓	
PDS	Use V12*		✓[I]			✓		✓[I]	✓	✓
C-SSRS	✓	✓[B,C,D]	✓[G]	✓[B,C,D]	✓[G]	✓	✓[B,C,D]	✓[G]	✓	✓
Administer Drug + Therapy		✓		✓			✓			
Monitoring of BP, Pulse, and Temp.		✓		✓			✓			
SUD		✓[D,E]		✓[D,E]			✓[D,E]			
Overnight Stay, SOCQ		✓		✓			✓			
Integrative Therapy Session			✓[A]		✓[A]			✓[A]		
Seven Days Telephone Contact			✓		✓			✓		
AEs Requiring Medical Attention	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Spont. Reported Reactions and all AEs		✓	✓[F]	✓	✓[F]		✓	✓[F]		
Changes in Tinnitus and/or Pain		✓[J,D]	✓[J,D]	✓[J,D]	✓[J,D]	✓[J]	✓[J,D]	✓[J,D]	✓[J]	✓[J]
AEs of psychiatric status or withdrawal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Perception of Experimental Sessions						✓			✓	
Complete Stage 2 go to follow-up									✓	
RRPQ									✓	
Issue Memory Aid Card									✓	
Follow-up Questionnaire										✓
Termination Visit										✓

* If Visit 18 is more than 8 weeks after Visit 12, then subjects will need to repeat measures prior to starting Stage 2.

A = First session is one day after experimental session; B = Approximately six hours post MDMA; C = At the beginning of the session; D = As needed; E = Approximately every 60 minutes; F = Reactions collected for seven days post experimental session; G =All visits and Day 2 and Day 7 phone calls only; H = One month after the second experimental session but before the third experimental session; I = On the day of the third integrative session; J = Only in subjects with pre-existing tinnitus and/or chronic pain.

6.0 Randomization and Blinding

Per Amendment 6, 26 subjects will be enrolled into the study. The randomized portion of the study will be blinded and there will be a 12:9:5 ratio between subjects in the active dose 1, active dose 2, and comparator dose treatment groups. Subjects will be assigned subject numbers, and subjects will be randomized in a blinded fashion.

7.0 Sample Size and Power Considerations

This study is a pilot investigation intended to gather preliminary data on the safety and efficacy of MDMA in 26 subjects with chronic, treatment-resistant PTSD. Because of their exploratory nature, pilot studies are often not powered for detecting the desired effect. Because it is a pilot study in a small sample, results will be used to collect effect size estimates for statistical power calculations for adequately powered subsequent studies.

8.0 Measures

8.1 Outcome Measures

Clinician-Administered PTSD Scale (CAPS-4) Global Severity Score, Diagnostic Criteria Met score, Associated Features

PTSD Diagnostic Scale (PDS), total score

Global Assessment of Functioning (GAF), total score

Beck Depression Inventory-II (BDI-II), total score

Post Traumatic Growth Inventory (PTGI), total score

Dissociative Experiences Scale-II (DES-II), total score

Pittsburgh Sleep Quality Index (PSQI), total score

States of Consciousness Questionnaire (SOCQ), total and composite scores

Long-term Follow-up Questionnaire (LTFU Questionnaire)

8.2 Safety Measures

Columbia Suicide Severity Rating Scale (C-SSRS)

Paced Auditory Serial Addition Test (PASAT)

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Subjective Units of Distress (SUD)

General Well-being (GWB)

Visual analog scale for Tinnitus and/or Pain visual analog scale

Vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body temperature (BT))

Adverse Events (AE), including Spontaneously Reported Reactions (SRR)

8.3 Process Measures

Therapist Adherence Criteria

Belief of Condition Assignment

Subject perceptions of experimental sessions

Reactions to Research Participation Questionnaire (RRPQ)

Qualitative Interviews

9.0 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. If a p-value less than 0.0001 occurs it 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 9.3 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.

9.1 Analysis Populations

Modified Intent-to-treat (mITT): all subjects who were randomized, received at least one experimental session and completed at least one outcome assessment

Per protocol (PP): all subjects who completed two experimental sessions and primary outcome assessment in Stage 1 and did not experience a major protocol deviation

Crossover: all subjects who completed Stage 2 in addition to completing Stage 1

Safety: all subjects who receive any study treatment

9.2 Handling of Dropouts, Missing Data

Subjects 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 subject 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.

9.3 Protocol Deviations

All protocol deviations will be included as a categorized listing. Safety and mITT analyses will include all enrolled subjects with all available data. Subjects with major deviations will be excluded from the per protocol analyses. Major deviations will be defined as anyone who was enrolled and has completed at least one experimental session but found to not meet inclusion/exclusion criteria during the course of the study. The number of subjects in each protocol deviation category listed below will be summarized by MDMA group, and individual subjects will be listed in the appendix.

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

Per Amendment 6, three subjects were found to have undisclosed exclusionary conditions during the course of their treatment in the study. As these conditions did not pose a safety risk, the subjects completed study procedures, but an additional three subjects were added to the total study enrollment. An additional two subjects withdrew or were withdrawn by the investigator prior to their second experimental session and were replaced per protocol. These subjects will be included in the Safety and mITT population.

9.4 Pooling of Investigator Centers

All subjects in this study come from one investigational center.

9.5 Baseline Values

Baseline values are from screening/baseline visit for all measures, except C-SSRS. 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 3), then 'baseline' scores will be visit 4 pre-drug C-SSRS observation.

9.6 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 in each treatment group and overall 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 displayed for each treatment group and overall together with reasons for early termination, where the percent is with respect to the total number of randomized subjects in that treatment group. The timepoint of doses and total MDMA (mg) administered will be summarized by treatment group for the Safety, mITT and PP Populations.

9.7 Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be summarized descriptively by treatment group and overall. The demographic data and baseline characteristics will be summarized for the mITT and Crossover Populations.

9.8 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 each treatment group. 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.

9.9 Efficacy Analyses

For all primary, secondary and exploratory endpoints descriptive statistics (n, mean, standard deviation, median, range, effect size (for measures of interest), or counts and percentages where appropriate) will be provided by treatment group.

Effect size (Cohen's *d*) for each treatment group will be determined by employing an independent-groups pretest-posttest design (IGPP), where the mean difference in the pretest-posttest is divided by the standard deviation of raw scores, and then the control group effect size is subtracted from the experimental group effect size [1].

$$d_{IGPP} = \frac{X_{postT} - X_{PreT}}{S_T} - \frac{X_{postC} - X_{PreC}}{S_C}$$

X = treatment means

S_T and S_C = pooled SD of pre- and post-test by group

9.9.1 Primary Efficacy Analyses

Clinician Administered PTSD Scale-4 (CAPS-4)

The primary efficacy evaluation is the change from baseline to the primary outcome timepoint (visit 12) in the CAPS-4 Global Severity score of PTSD (difference score). The primary efficacy comparison will be made with ANOVA at an alpha level of 0.05. If the primary hypothesis rejects, pairwise comparisons among the treatment groups will be made with t-tests. If the parametric assumptions for the ANOVA and t-test analyses are not met, the analogous nonparametric methods will be used (Kruskall-Wallis, Wilcoxon Rank-Sum).

9.9.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be made with ANOVA comparing change from baseline (Baseline) to the primary outcome timepoint (visit 12) of all the secondary measures, following the same methodology used for the primary endpoint. If the parametric assumptions for the ANOVA analyses are not met, the analogous nonparametric methods will be used (Kruskall-Wallis, Wilcoxon Rank-Sum).

PTSD Diagnostic Scale (PDS) total score will be analyzed in the same manner as the CAPS-4 global scale primary analysis.

Global Assessment of Functioning (GAF) total score will be analyzed in the same manner as the CAPS-4 global scale primary analysis.

Beck Depression Inventory-II (BDI-II) total score will be analyzed in the same manner as the CAPS-4 global scale primary analysis.

Post Traumatic Growth Inventory (PTGI) total will be analyzed in the same manner as the CAPS-4 global scale primary analysis.

Dissociative Experiences Scale-II (DES-II) total will be analyzed in the same manner as the CAPS-4 global scale primary analysis.

Pittsburgh Sleep Quality Index (PSQI) global scores will be analyzed in the same manner as the CAPS-4 global scale primary analysis.

9.9.2.1 Secondary Efficacy Analyses at Secondary Endpoints

Assess 3 vs. 2 experimental MDMA sessions
For the CAPS, the absolute changes in the measure from the primary endpoint to end of Stage 1 for the 100 and 125 mg groups will be compared with t-tests. In the crossover subjects (40 mg) the absolute changes in the measures from the secondary (visit 27) endpoint to end of Stage 2 (visit 32) will be compared with t-tests.

Crossover Subject Analyses
CAPS data from subjects assigned to the 40 mg group in Stage 1, i.e. 'crossover population,' will be analyzed by t-tests on difference scores from primary endpoint (visit 12) in Stage 1 to secondary endpoint in Stage 2 (visit 27). Additionally, the following measures' total scores will be analyzed in this same fashion: CAPS, PTGI, BDI-II, GAF, PSQI, DES-II, PDS.

Long-term Follow-up
For the CAPS, PDS, PTGI, BDI-II, GAF, PSQI, and DES-II, the absolute changes in the measures from baseline to the long-term follow-up visit (one year post final experimental year) will be compared with t-tests. The absolute changes in the measures from long-term follow-up to End of Stage 1 (visit 17, 100 mg and 125 mg) or long-term follow-up compared to End of Stage 2 (visit 32, 40 mg) will be compared with t-tests.

9.9.3 Exploratory Analyses

Clinician Administered PTSD Scale-4 (CAPS-4)

- The percentage of subjects who achieve a 30% drop in CAPS-4 global score at the primary endpoint (visit 12) will be an indirect measure of clinical significance. Descriptive statistics will be computed and displayed by Stage 1 treatment groups.

- The percentage of subjects who no longer meet PTSD diagnostic criteria according to the CAPS-4 at the primary endpoint (visit 12) will be an indirect measure of clinical significance. Descriptive statistics will be computed and displayed by Stage 1 treatment groups.

- CAPS-4 Subscale Scores (B, C, D, F) at the primary endpoint (visit 12) will be analyzed in the same manner as the primary analysis of the global score. Descriptive statistics will be computed and displayed by Stage 1 treatment groups.

- Active dose 1 (125mg) and Active dose 2 (100mg) CAPS data at the primary endpoint will be tested for equivalence using confidence intervals. If the two groups are found to be equivalent, then outcomes for the active dose groups will be combined and will be tested for significant differences from the comparator group using difference scores in independent sample t-tests, with p value set at 0.05.

- Comparison of the effect of a third experimental session with either Active dose 1 or Active dose 2 may be conducted if sufficient group sizes are attained, and analyses comparing outcomes at third session may be conducted with and without Active dose 2 participants who elected to take Active dose 1 during the third experimental session.

- Two regression analyses will be conducted using (1) all subjects with a Frequency score of 2 or greater and an Intensity score of 2 or greater on the CAPS Associated Features 29 or 30 at baseline and (2) baseline DES-II total score as baseline covariates to determine whether the dissociative subtype of PTSD is predictive of treatment outcomes.
- Here is my suggestion for wording the bullet point above: To determine if baseline variables that assess disassociation are predictive of CAPS Global Severity Score at the Primary Endpoint (dependent variable), a multiple regression analysis will include the following independent variables at baseline (1) dichotomous variable defined as Frequency of 2 or greater and Intensity of 2 or greater on the CAPS Associated Features 29 or the alternative (2) dichotomous variable defined as Frequency of 2 or greater and Intensity of 2 or greater on the CAPS Associated Features 30 or the alternative, and (3) DES-II total score.
-

PTSD Diagnostic Scale (PDS)

A repeated measures analysis of variance (ANOVA) will be performed upon PDS scores at baseline, after experimental sessions (visits 4 and 13) and at the end of Stage 1 (visit 17), with p value set at 0.05. Stage I treatment group will serve as a between-subjects factor. Results of repeated measures ANOVA analysis will be used to examine the effects of each experimental session on self-reported PTSD symptom severity.

Clinician Administered PTSD Scale-4 (CAPS-4) and PTSD Diagnostic Scale (PDS)

PDS and CAPS scores will be correlated via Pearson's product moment correlation at baseline and the timepoint that the primary efficacy is measured to provide a comparison of a self-report measure with a clinician-administered measure of PTSD symptoms.

9.9.3.1 Process Measures

States of Consciousness Questionnaire (SOCQ)
Descriptive statistics will be computed for SOCQ scores completed after each MDMA-assisted psychotherapy session, and SOCQ scores will be compared by initial dose using ANOVA for overall differences and t-tests for pairwise comparisons for each experimental session. The data will be explored for effects of dose on composite and total SOCQ scores.

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.

Belief of Condition Assignment
In order to compare the therapists', independent raters', and subjects' belief of treatment group to actual MDMA dose received in each blinded session, the number and frequency of correct guesses will be calculated and depicted by dose group and study role (subject and each therapist).

Subject's Perceptions of Experimental Sessions
Descriptive statistics will be calculated for subject's perceptions of experimental sessions. Mean, standard deviation and range of individual responses and sum of items #1-4 will be examined. For the 100 and 125 mg group, within-subjects t-tests will be performed on subject's perceptions at Stage 1 primary (visit 12) and end of stage 1 (visit 17) endpoints. The same analysis will be performed for 40 mg group, but data will be from Stage 2 secondary (visit 27) and end of stage 2 (visit 32) endpoints.

Reactions to Research Participation Questionnaire (RRPQ)
Frequency of response will be tabulated for 'reasons for participation' across Stage 1 treatment groups. Descriptive statistics will be computed for total scores for subscales and displayed by Stage 1 conditions.

Adherence to the Treatment Manual
The sponsor will collect ratings of adherence to the treatment manual from specifically selected types of sessions. Descriptive statistics will be computed for each adherence scale within a given session. If sufficient data is available, the sponsor will correlate the mean adherence ratings for adherence scale and session type with Global CAPS scores from the closest available endpoint assessment to investigate the effects of adherence to the treatment manual on reduction in PTSD symptoms. If it is found that there are specific factors within the adherence scales, then the factor will be correlated with Global CAPS score.

Qualitative Interviews
Qualitative interviews conducted by a researcher who is part of the study team during the 12-month follow-up visit will be transcribed to text. A computer-assisted qualitative data analysis software package will be utilized to assist in thematic content analysis of the interview transcripts. A member of the research team will code the interviews for content, to identify emerging themes and organize data into thematic constructs utilizing a grounded theory approach. Descriptive statistics will be calculated for emerging themes.

9.9.4 Safety Analyses

The primary measure of safety will be the reporting of adverse events. The Adverse events considered 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 Stage I treatment group and by system organ class. AEs will also be summarized by severity and relationship to study drug. Subject incidence of SAEs by Stage I treatment group 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 Stage 1 treatment group.

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 [2]. A positive response for suicidal ideation is counted when a subject 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 score. Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a subject 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 score. The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated by Stage I treatment group and time period. Compare lifetime serious suicidal ideation and positive behavior frequencies to cumulative frequencies anytime during the study until end of Stage 1 and Stage2.

Subjective Units of Distress (SUD)

Descriptive statistics for SUD scores will be calculated by Stage 1 treatment group and time period with counts and percentages.

Visual analog scale for Tinnitus and/or Pain visual analog scale

Formal analysis of Changes in Tinnitus and/or Pain visual analog scale scores will only occur if three or more subjects complete Changes in Tinnitus and/or Pain visual analog scale at baseline and primary endpoint. Likewise, formal between-groups analyses will not be performed if all primary endpoint scores are from subjects assigned to the same treatment group. Descriptive statistics will be presented on the difference between baseline and primary endpoint changes in Tinnitus and/or Pain visual analog scale scores in the full dose and comparator dose treatment groups.

Vital signs

Vital signs (heart rate, body temperature, systolic and diastolic blood pressure) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Occurrences of systolic and diastolic blood pressure, heart rate, and body temperature readings above the pre-determined cutoff will be displayed with numbers and percentages by timepoint.

Paced Auditory Serial Addition Test (PASAT) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

RBANS and PASAT scores at baseline and primary endpoint will be compared in each active dose group and comparator dose groups using descriptive statistics. In an exploratory analysis, the effects of maximal exposure to MDMA on neurocognitive function using the RBANS and PASAT will be examined.

9.10 Timing of Analyses

The primary efficacy analysis will be conducted after all subjects complete Stage 2, but before all long-term follow-up data have been collected. 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.

10.0 Statistical Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.3 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.

11.0 References

References

1. Kadel, R. and K. Kip. *A SAS macro to compute effect size (Cohen'sd) and its confidence interval from raw survey data*. in *Proceedings of the Annual Southeast SAS Users Group Conference*. 2012.

2. 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.