MP-4 Statistical Analysis Plan
Version 1: 31 May 2016

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USE	In conjunction with relevant FDA guidance
STUDY TITLE	A Randomized, Double-Blind, Controlled Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada
LATEST PROTOCOL	Amendment 2 Version 3, June 20, 2014
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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
GAF	Global Assessment of Functioning
GWB	General Well-being
HR	Heart Rate
mITT	Modified Intent To Treat
MAPS	Multidisciplinary Association for Psychedelic Studies
MDMA	3,4-methylenedioxymethamphetamine
MPBC	MAPS Public Benefit Corporation
NEO PI	Neuroticism-Extroversion-Openness Personality Inventory
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-4, a Phase 2 pilot clinical trial designed to evaluate the safety and effect of MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD. Though the protocol states 12 subjects will be enrolled, the study concluded with 6 subjects treated.

Due to the reduction in sample size from 12 to 6, the planned statistical analyses described in the protocol were not executed. This document presents a revised plan appropriate for the 6 subjects enrolled. The background provided in sections 3-5 below are based on information in the last approved protocol, they have not been adjusted based on the change in enrollment which was discontinued at N=6 subjects. This SAP will be finalized prior to any unblinded, inferential or descriptive analyses of data pertaining to the MAPS MP-4 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 effect 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. MDMA (125 mg) and an inactive placebo (0 mg) will be assessed in two Stage 1 sessions. Subjects who received the inactive placebo 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. Subjects that receive 125 mg MDMA in Stage 1 will have one additional open-label active dose session. Co-therapist teams will conduct the study.

This study is designed to obtain estimates of effect size and collection of safety data. 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 subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

4.2 Secondary Objectives

- 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 (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) 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 Dissociation 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, changes in personality via NEO-PI 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, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI one year after the final experimental session for each subject.

The following objectives will include exploratory analyses intended to inform 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 full dose subjects in Stage 1 and Stage 2 using CAPS, PDS, BDI-II, GAF, PSQI, PTGI, NEO-PI, and DES-II.
- Assess the ability of the therapists and subjects to accurately guess condition 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 the safety of subjects during and after the experimental sessions by assessing physiological effects, psychological distress, adverse events, spontaneously reported reactions and suicidality.

- Vital signs (blood pressure, heart rate, and temperature) and Subjective Units of Distress (SUD) will be measured during each experimental session. Comparisons will be made for SUD scores and vital signs between each condition.
- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.
- 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 condition, and end of Stage 1/end of Stage 2 for maximal exposure.

- 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.

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, active placebo controlled study of MDMA-assisted psychotherapy in subjects diagnosed with chronic, treatment-resistant PTSD of at least six-months duration. The schedule will include two blinded MDMA-assisted psychotherapy sessions in Stage 1 scheduled approximately one month apart with a male/female co-therapist team. Subjects will remain with only one team for the entirety of the study. Upon enrollment, subjects will meet with their therapist team for 3 preparatory sessions. Each MDMA-assisted psychotherapy session will be followed by an overnight stay at the clinic, an integrative psychotherapy session the next day, and daily telephone calls for the next seven days. Experimental sessions will be followed by two additional integrative sessions. 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 be evaluated for long-term effects 12 months after their last experimental session (See Table 2 Time and Events).

In Stage 1, subjects will be randomly assigned to receive two blinded experimental psychotherapy sessions assisted by either inactive placebo or full dose MDMA. The blind will be broken for all subjects in Stage 1 after completing the primary endpoint assessment, 1-month after the second experimental session in Stage 1. After unblinding, active dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. Subjects who receive the placebo dose of MDMA will be offered the option to enroll in the open-label Stage 2 unless they meet any exclusion criteria for study participation. In Stage 2, subjects will receive full dose MDMA and the three experimental sessions will otherwise follow the same sequence of events after a single preparatory session (See Time and Events Table). All subjects will complete a follow-up occurring 2 months after their last experimental session in Stage 1 and Stage 2, as 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.

Table 1: Dose Regimen

Stage 1 Experimental Sessions	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose	Min-Max Cumulative Dose with Titration
1 and 2	Comparator Dose	0 mg	0 mg	0 mg	
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg	
Stage 2 Experimental Sessions					
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

Table 2. Time and Event 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/Baseline	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Experimental	Integrative	Outcome
Visit Timing – see Section 7.3 for visit windows	Up to 2 months prior to V1	Between baseline and V4	within 13 weeks post CAPS	Between V4 and V8	2-5 weeks post V4	Between V8 and V12	3-5 weeks post V8	3-5 weeks post V8	Between V13 and V17	7-10 weeks post V13
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Physical Exam, ECG	✓									
Brief Neurological Exam	✓									
SCID-RV (IR)	✓									
Clinical Lab Tests with HIV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication Taper (if applicable)		✓								
Study Enrollment (if eligible)		✓[O]								
Record to Audio/Video		✓	✓	✓	✓	✓		✓	✓	
General Wellbeing		✓	✓	✓	✓	✓	✓	✓	✓	
Drug Screen	✓		✓		✓			✓		
Pregnancy Screen (if applicable)	✓		✓		✓			✓		
Obtain Container Assignment			✓[B]		✓[B]					
CAPS, GAF, BDI-II, NEO-PI, PSQI, PTGI, DES-II	✓						✓[L]			✓[Q]
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			✓[F, E]		✓[F, E]			✓[F, E]		
Belief of Condition Assignment				✓[K]		✓[K]				
Overnight Stay, SOCQ			✓		✓			✓		
Integrative Therapy Session				✓[A]		✓[A]			✓[A]	
7 Days Integrative 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 LTFU; I = Every face to face visit 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 = After unblinding for full dose subjects only; O = Only on Visit 1; P = Only in subjects with pre-existing tinnitus and/or chronic pain; Q = All measures listed except for the NEO-CI.

Time and Events Stage 2	**Preparatory Sessions**	**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 – See Section 7.3 for visit windows	Within 1 month post V12*	+/_1 week post V18	Between V19 and V23	2-5 weeks post V19	Between V23 and V27	3-5 weeks post V23	3-5 weeks post V23	Between V28 and V32	7-10 Weeks 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 Wellbeing	✓	✓	✓	✓	✓	✓	✓	✓		
Drug Screen		✓		✓			✓			
Pregnancy Screen (if applicable)		✓		✓			✓			
CAPS, GAF, BDI-II, NEO-PI, PSQI, 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]		
7 Days Integrative 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,D]	✓[J,D]	✓[J,D]	✓[J, D]	✓[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 with the exception of NEO-PI.

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 = Every face to face visit 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; K = All measures listed except for the NEO-PI

6.0 Randomization and Blinding

The protocol states in total, 12 subjects will be enrolled and randomized in Stage 1. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the Full Dose and Comparator dose groups. Subjects will be assigned subject numbers, and subjects will be randomized in a blinded fashion. At the conclusion of enrollment, six subjects were enrolled in a 4:2 ratio between subjects in the Full Dose and Comparator Dose groups.

7.0 Sample Size and Power Considerations

This study is a pilot investigation intended to gather preliminary data on the safety and effect of MDMA in 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

Post Traumatic Growth Inventory (PTGI), total score

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

Pittsburgh Sleep Quality Index (PSQI), total score

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

NEO Personality Inventory (NEO PI), five factors

8.2 Safety Measures

Columbia Suicide Severity Rating Scale (C-SSRS)

Subjective Units of Distress (SUD)

General Well-being (GWB)

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Paced Auditory Serial Addition Test (PASAT)

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

Belief of Condition Assignment

Therapist Adherence Criteria

Subject perceptions of experimental sessions

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

Reactions to Research Participation Questionnaire (RRPQ)

Long-term Follow-up Questionnaire (LTFU Questionnaire)

9.0 Analyses

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, and approximately normal variables will be described using sample mean and standard deviations. Although the protocol plan specifies parametric t-tests and ANOVAs, the small group sizes (n=2 and n=4) are insufficient for analysis. Therefore, this statistical analysis plan acts to amend the data analysis plan in the protocol to use group descriptives and subject listings.

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

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

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 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

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 enrollment 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 Analyses of Effect

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

Since the study ended with insufficient group sizes (n=2 and n=4), no formal analyses will be performed.

9.9.1 Primary Analyses of Effect

<u>Clinician Administered PTSD Scale-4 (CAPS-4)</u>

The primary evaluation is the change from baseline to the primary outcome timepoint (visit 12) in the CAPS-4 Global Severity score of PTSD (difference score). Data will be presented with descriptive statistics and subject listings.

9.9.2 Secondary Analyses of Effect

The secondary analyses will be presented as change from baseline (Baseline) to primary endpoint (visit 12) of all the secondary measures, following the same methodology used for the primary endpoint.

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

Global Assessment of Functioning (GAF) total score will be summarized 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.

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

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

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

NEO Personality Inventory (NEO PI) five factor scores will be analyzed in the same manner as the CAPS-4 global scale primary analysis.

9.9.2.1 Secondary Analyses of Effect at Secondary Endpoints

Crossover Subject Analyses
Formal statistical comparisons between Stage 1 and Stage 2 scores may only occur if all three eligible participants enroll in Stage 2. As only two subjects completed Stage 2, no formal statistical comparisons will be conducted within-subjects.

Long-term Follow-up
For the CAPS, PDS, GAF, PTGI, BDI-II, PSQI, and DES-II the absolute changes in the measures from baseline to the long-term follow-up visit (one year post final experimental session) will be summarized. The absolute changes in scores on measures from long-term follow-up to End of Stage 1 (full dose group) or long-term follow-up compared to End of Stage 2 (comparator group) will be presented.

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), end of Stage 1, and end of Stage 2 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), end of Stage 1, and end of Stage 2 will be an indirect measure of clinical significance. Descriptive statistics will be computed and displayed by Stage 1 treatment groups.

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 presented by treatment group.

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' and subjects' belief of treatment group to 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).

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.

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. No formal analyses will be conducted due to small sample size.

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. Due to insufficient sample size, the sponsor will not 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.

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 treatment group by stage and by system organ class. AEs will also be summarized by severity and relationship to study drug. Subject incidence of SAEs by 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 [1]. 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 Stage 2.

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.

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.

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

Changes in Tinnitus and/or Pain visual analog scale scores will presented with descriptive statistics at each endpoint.

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 summarized by the active and comparator dose groups using descriptive statistics.

9.10 Timing of Analyses

The primary analysis may be conducted after all eligible 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 the 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. 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.