
# MP-8 Statistical Analysis Plan

## Version 1: 06 October 2015

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| CORPORATION DESIGNEE | Amy Emerson<br>Executive Director and Director of Clinical Research |
| USE | In conjunction with relevant FDA guidance |
| STUDY TITLE | A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD) |
| LATEST PROTOCOL | Amendment 5 Version 1, August 14, 2013 |
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## 1.0 List of Abbreviations and Definitions of Terms

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

*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 End of Stage 1 score, used to test for differences between and within groups to determine change as a function of experimental treatment over time

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

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

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

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

*Process measures:* study measures or qualitative observations collected during the study that may increase depth of understanding and that are not necessarily related to safety or efficacy

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

*Safety:* assessment of the condition of study subjects that examines potential risks, adverse events, and reactions

*Safety measures:* study measures that assess safety, such as heart rate monitoring, that are used to assess safety of the study drug

*Spontaneously reported reactions, reactions:* specific expected reactions gathered from the literature on MDMA

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

*Tabular listing:* list of each variable or item for each individual subject either in total or by condition in a table format

## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| BDI-II | Beck Depression Inventory-II |
| 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 |
| ITT | Intent To Treat |
| MAPS | Multidisciplinary Association for Psychedelic Studies |
| NEO PI | Neuroticism-Extroversion-Openness Personality Inventory |
| PP | Per Protocol |
| PTSD | Posttraumatic Stress Disorder |
| PSQI | Pittsburgh Sleep Quality Index |
| PTGI | Post Traumatic Growth Inventory |
| RCT | Randomized Controlled Trial |
| RRPQ | Reactions to Research Participation Questionnaire |
| SBP | Systolic Blood Pressure |
| SOCQ | States of Consciousness Questionnaire |

## 2.0 Introduction

This document contains a Statistical Analysis Plan for the study, "A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)."

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)-assisted psychotherapy in persons with posttraumatic stress disorder (PTSD).

Encouraging data has been obtained from MAPS' completed United States (U.S.) pilot studies, MP1 and MP2. MAPS is currently sponsoring other Phase 2 studies in the U.S., Israel, and Canada. Ongoing and planned Phase 2 studies are laying the groundwork for an eventual End-of-Phase 2 meeting with FDA and possible Phase 3 multi-site MDMA/PTSD research studies.

This study, MP-8, will examine the safety and efficacy of MDMA-assisted psychotherapy in 24 veterans, firefighters or police officers with service-related PTSD, and will seek to enroll roughly equal numbers of men and women. This study will include those with chronic PTSD of at least six months duration who satisfy PTSD diagnostic criteria despite having received prior treatment with either medication or psychotherapy. Full, medium and low dose MDMA will be assessed in Stage 1, as well as the benefit of three vs. two full dose sessions. Subjects who received the medium and low 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.

MAPS' initial U.S. pilot study, conducted at the same site as this study, enrolled 23 subjects, of which 20 were evaluable, with a majority of whom were women suffering from PTSD related to sexual assault and/or childhood sexual abuse (N=18) [1, 2]. Only two subjects had PTSD from war-related trauma (U.S. veterans of the Iraq War) and both were male. According to the European Medicines Agency (EMA) Guideline for the Development of Medicinal Products for the Treatment of PTSD, it is desirable to examine treatment response in homogenous samples, conducting separate trials for different populations. The findings from this study in veterans, firefighters and police officers with service related trauma will be compared with results from our initial U.S. pilot study, mostly in women survivors of sexual abuse and assault.

In order to refine our triple-blind methodology, MP-8 will evaluate three different doses of MDMA to determine their relative success in achieving blinding of therapists, subjects, and independent raters.

In addition, this will be the first study of MDMA-assisted psychotherapy to permit the enrollment of subjects with two medical conditions that were exclusion criteria in the previous trial: Hepatitis-C, and controlled hypertension. Should any subjects with these conditions seek enrollment in the study, they will be required to go through additional specified screening procedures and additional monitoring for safety during the experimental sessions.

# 3.0 Study Objectives

## 3.1 Primary Objective

- Assess changes in PTSD symptoms via Clinician-Administered PTSD Scale (CAPS-4) global scores in subjects receiving by condition in the randomized study arms at baseline and the primary endpoint, one month after the second experimental session.

## 3.2 Secondary Objectives

The following objectives will compare full, medium and low dose subjects in the blinded portion of Stage 1:

- Assess changes in posttraumatic growth via Post Traumatic Growth Inventory (PTGI) scores from baseline to the primary endpoint.
- Assess changes in global functioning via Global Assessment of Functioning (GAF) scores from baseline to the primary endpoint.
- Assess changes in symptoms of depression via Beck Depression Inventory-II (BDI-II) scores from baseline to the primary endpoint.
- Assess changes in self-reported sleep quality via the Pittsburgh Sleep Quality Index (PSQI) from baseline to the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociative Experiences Scale-II (DES-II) from baseline to the primary endpoint.
- Assess changes in Neuroticism-Extroversion-Openness Personality Inventory (NEO PI) scores from baseline to the primary endpoint.

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

- Explore the effects of each MDMA-assisted psychotherapy 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 effects of a third active dose experimental session by comparing Global CAPS, BDI-II, GAF, PSQI, PTGI (in reference to start of the study), and DES-II scores at the primary/secondary endpoint and end of Stage 1/ Stage 2 in subjects receiving a third experimental session in Stage 1 and Stage 2.
- Assess the ability of the investigators and subjects to accurately guess condition assignment when asked to do so after each blinded experimental session.
- Assess value of third experimental session in Stage 1/Stage 2 by collecting each active dose subject's perception of experimental sessions at the primary/secondary endpoint and end of Stage 1/ Stage 2.
- Correlate adherence to the Treatment Manual with Global CAPS scores using adherence criteria ratings to assess videos of psychotherapy sessions.
- Assess PTSD symptoms via CAPS, posttraumatic growth via PTGI, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, dissociation symptoms via DES-II, and personality via NEO PI throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of receiving active dose MDMA on PTSD symptoms via CAPS, posttraumatic growth via PTGI, personality changes via NEO PI, depression

symptoms via BDI-II, global functioning via GAF, and sleep quality via PSQI one year after the final experimental session for each subject.

### 3.3 Safety Objectives

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) before, during and after experimental sessions and on selected days of telephone or face-to-face contact, with comparisons made between subjects in each condition.
- Subjective Units of Distress (SUD) and vital signs (blood pressure, heart rate and temperature) will be measured during each experimental session, and comparisons will be made for vital signs between conditions.
- 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 according to Section 8.3

## 4.0 Study Design

This randomized, triple-blind study will examine the safety and efficacy of MDMA-assisted psychotherapy with 30, 75 or 125 mg MDMA in twenty-four veterans, firefighters and police officers diagnosed with chronic, treatment-resistant PTSD arising from their service. These subjects will ideally, but not necessarily, include twelve men and twelve women. Supplemental doses of half the initial dose may be administered between 1.5 and 2.5 hours after the initial dose was administered.

Prior to undergoing the first MDMA-assisted (experimental) session, all subjects will undergo three 90-minute preparatory non-drug psychotherapy sessions with a male and female co-therapist team. Stage 1 of the study will consist of two blinded experimental sessions and, for the full dose group, one open-label experimental session, each lasting six to eight hours and scheduled three to five weeks apart. Experimental sessions will follow a similar sequence of events. (See Time and Events Table). A co-therapist team will perform all non-drug and MDMA-assisted psychotherapy sessions in their outpatient office. Subjects will complete the SOCQ, a measure of alterations in consciousness related to mystical experiences, during the period of time between the end of each MDMA-assisted psychotherapy session and before they leave the treatment facility the next day. Subjects will remain at the study site overnight accompanied by an attendant. Subjects will undergo three integrative psychotherapy sessions after each experimental session, with the first integrative session occurring on the day after the experimental session. All psychotherapy sessions may be recorded to audio and video.

A blinded independent rater, who will not be present during any psychotherapy sessions, will assess subject PTSD symptoms with CAPS, symptoms of depression with BDI-II, posttraumatic growth with PTGI, global functioning with GAF, sleep quality with PSQI, and dissociation with the DES-II. Changes in personality traits will be assessed via NEO-PI. Outcome assessments will be done at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at the 12-month follow-up and at equivalent points in Stage 2.

When each subject completes the evaluation at the primary endpoint, the blind will be broken for that subject. Subjects who had been assigned to receive low dose or medium dose MDMA will subsequently have the opportunity to enroll in the open-label study arm, or "Stage 2." Stage 2 must start within a maximum of 5 months after the subject finishes Stage 1. The open-label study arm will follow a similar sequence of events and procedures, except that there will be a single preparatory session, and all three MDMA-assisted psychotherapy sessions will be open-label. Subjects will receive an initial dose of 100 mg MDMA in the first experimental session, and one of two active doses of MDMA that are clinically titrated by the CI during the second and third open-label experimental sessions that will otherwise follow the same sequence of events (See Time and Events Table). Outcome measures except for the NEO PI will be repeated one month after the second Stage 2 experimental session, and all outcome measures will be repeated at the end of Stage 2.

The study will conclude with a one-year follow-up occurring 12 months after the final experimental session of Stage 1 for subjects who received full dose MDMA or who elected not to enroll in Stage 2 after receiving either the medium or low doses in Stage 1. Subjects who enrolled in Stage 2 will have their final follow-up 12 months after the final open-label experimental session. Outcome measures will be repeated at the 12-month follow-up, as well as a questionnaire concerning self-reported long-term effects of study participation.

Sub-studies in a select group of subjects in this study may be conducted for exploratory purposes. Subjects will complete a separate consent process if they chose to participate in these studies.

**Table 4.0-1: Stage 1 Blinded Drug Doses**

| Condition | Number of Subjects | Initial Dose | Supplemental Dose | Min-Max Cumulative Dose |
|---|---|---|---|---|
| *Low Dose* | 6 | 30 mg | 15 mg | 30-45 mg |
| *Medium Dose* | 6 | 75 mg | 37.5 mg | 75-112.5 mg |
| *Full Dose* | 12 | 125 mg | 62.5 | 125-187.5 mg |

**Table 4.0-2: Stage 2 Drug Doses**

| Experimental Session | Dose | Initial Dose | Optional Supplemental Dose | Min-Max Cumulative Dose | Min-Max Cumulative Dose with Titration |
|---|---|---|---|---|---|
| 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 |

For further details please refer to the protocol Section 5.0 Protocol.

| **Table 4.1: Stage 1 Time & Events** | **Screen/Baseline** | | **Preparatory** | **Experimental Session 1** | | **Experimental Session 2** | | | **Experimental Session 3** | | **Follow-Up** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit # | Pre-Study | V1 | V 2,3,4 | V5 | V 6,7,8 | V9 | V 10,11,12 | V13 | V14 | V 15,16,17 | V18 |
| Type of Visit | Screening may take place over more than one day | Enrollment | Preparatory Sessions | Experimental Session 1 | Integrative Sessions | Experimental Session 2 | Integrative Sessions | Primary Endpoint | Experimental Session 3 | Integrative Sessions | End of Stage 1 & Outcome |
| Visit Timing or Study day or Window | Up to 2 months prior to Visit 1 | | Prior to V5 [M] | Up to 7 weeks post V1 | Before V9 [A] | 3-5 weeks post V5 | Before V13 [A] | 1 month post V9 | 3-5 weeks post V9 [N] | Before V18 [A, N] | May happen over > 1 day. 2 mo. post V14 [N] |
| Initial Phone Screen | X | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | |
| Medical/Psychiatric History | X | | | | | | | | | | |
| General Phys. Exam (BP, Heart rate, Temp) | X | | | | | | | | | | |
| Brief Neurological Exam | X | | | | | | | | | | |
| ECG | X | | | | | | | | | | |
| SCID-I-RV | X | | | | | | | | | | |
| Clinical Lab Tests, w/ HIV, HCV test | X | | | | | | | | | | |
| Collect Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X |
| Medication Taper (if applicable) | X | X | | | | | | | | | |
| Study Enrollment after meeting I/E | | X | | | | | | | | | |
| Record to Audio/Video | X [L] | | X | X | X | X | X | X [L] | X | X | X [L] |
| General Well-Being | | X | X | X | X | X | X | | X | X | |
| Drug Screen | X | | | X | | X | | | X | | |
| Pregnancy Screen (if applicable) | X | | | X | | X | | | X | | |
| Complete Randomization Procedure | | | | X [B] | | | | | | | |
| CAPS, GAF, BDI-II, PTGI, PSQI, DES-II (IR) | X | | | | | | | X | | | X |
| NEO PI (Ind. Rater) | X | | | | | | | X | | | |
| C-SSRS | | X | X | X [C, D, E] | X [I] | X [C, D, E] | X [I] | X | X [C, D, E] | X [I] | X |
| Administer IP Drug + Therapy, SOCQ | | | | X | | X | | | X | | |
| Monitoring of BP, Heart rate and Temp. | | | | X | | X | | | X | | |
| SUD | | | | X [F, E] | | X [F, E] | | | X [F, E] | | |
| Beliefs of Condition Assignment | | | | | X [K] | | X [K] | | | X [K] | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overnight Stay | | | | X | | X | | | X | | |
| Integrative Therapy Session | | | | | X | | X | | | X | |
| 7 days Integrative Telephone Contact | | | | | X [I] | | X [I] | | | X [I] | |
| AEs Requiring Medical Attention | | | | X | X | X | X | X | X | X | X |
| Spont. Reported Reactions and all AEs | | | | X | X | X | X | | X | X | |
| Changes in Tinnitus and/or Pain | X [O] | | X [E, O] | X [E, O] | X [E, O] | X [E, O] | X [E, O] | X [O] | X [E, O] | X [E, O] | X [O] |
| AEs of psychiatric status or withdrawal | | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | | X | X | X | X | X | X | X | X | X | X |
| Issue Memory Aid Card [H] | | | | | | | | | | | X |
| Unblinding [J] | | | | | | | | X | | | |
| Perception of Third Session | | | | | | | | X [N] | | | X [N] |
| RRPQ | | | | | | | | | | | X [H] |

A =First Integrative session is 1 day after exp session B = At least 24 hrs prior to 1st exp. session C =Approximately 6 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 meds are tapered (V3) H = Only for subjects starting Long term Follow up and not going to Stage 2 I =For 7 days post Exp. Session, C-SSRS D2 and D7 of calls only, General well being for all 7 days J =Subjects in the medium or low dose group will not have visits 14-18, but will instead move onto Stage 2. K= On the day of the 1st integrative session following the Exp. Session L=CAPS may be videotaped M=First preparatory session (V2) may happen at the time of screening, before enrollment. N= Full dose subjects only. O= Only in subjects with pre-existing tinnitus and/or chronic pain.

| **Table 4.1: Stage2 Time & Events** | **Preparatory** | **Experimental Session 1** | | **Experimental Session 2** | | | **Experimental Session 3** | | **Follow-Up** | **Long Term Follow up after Stage 1 or Stage 2** | **Long Term Follow-Up** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit # | V19* | V20 | V 21,22,23 | V24 | V 25,26,27 | V28 | V29 | V 30,31,32 | V33 | | 1 Year Follow-up |
| Type of Visit | Preparatory Session | Experimental Session 1 | Integrative Sessions | Experimental Session 2 | Integrative Sessions | Secondary endpoint | Experimental Session 3 | Integrative Sessions | End of Stage 2 & Outcome | | Follow-Up & Outcome |
| Visit Timing or Study day or Window | Within maximum of 5 months of V13* | After V19 | Before V24 [A] | 3-5 weeks post V20 | Before V28 [A] | 1 month post V24, beforeV 29 | 3-5 weeks post V24 | Before V33 [A] | May happen over > 1 day 2 months post V29 | | May happen over > 1 day. One Year post V14 or V29 |
| Confirm Informed Consent | X | | | | | | | | | | |
| Confirm Inclusion/Exclusion | X | | | | | | | | | | |
| Enrollment in Stage 2 | X | | | | | | | | | | |
| Collect Concomitant Medication | X | X | X | X | X | X | X | X | X | | X |
| Record to Audio/Video | X | X | X | X | X | X[H] | X | X | X[H] | | |
| General Well-Being | X | X | X | X | X | | X | X | X | | |
| Drug Screen | | X | | X | | | X | | | | |
| Pregnancy Screen (if applicable) | | X | | X | | | X | | | | |
| CAPS, GAF, BDI-II, PTGI, PSQI, DES-II (IR) | Use V13* | | | | | X | | | X | | X |
| NEO PI with Ind. Rater | Use V13* | | | | | | | | X | | X |
| C-SSRS | X | X[C, D, E] | X[G] | X[C, D, E] | X[G] | | X[C, D, E] | X[G] | X | | X |
| Administer IP Drug + Therapy, SOCQ | | X | | X | | | X | | | | |
| Monitoring of BP, Heart rate and Temp. | | X | | X | | | X | | | | |
| SUD | | X[D, F] | | X[D, F] | | | X[D, F] | | | | |
| Overnight Stay | | X | | X | | | X | | | | |
| Integrative Therapy Session | | | X | | X | | | X | | | |
| 7 days Integrative Telephone Contact | | | X[G] | | X[G] | | | X[G] | | | |
| AEs Requiring Medical Attention | X | X | X | X | X | X | X | X | X | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Spont. Reported Reactions[G] and all AEs | | X | X[G] | X | X[G] | | X | X[G] | | | |
| Changes in Tinnitus and/or Pain | | X[D, I] | X[D, I] | X[D, I] | X[D, I] | X[I] | X[D, I] | X[D, I] | X[I] | | X[I] |
| AEs of psychiatric status or withdrawal | X | X | X | X | X | X | X | X | X | | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | | X |
| Perception of Third Session | | | | | | X | | | X | | |
| Complete Stage 2, go to 1yr F/U | | | | | | | | | X | | |
| RRPQ | | | | | | | | | X | | |
| Issue Memory Aid Card | | | | | | | | | X | | |
| Follow-up Questionnaire | | | | | | | | | | | X |
| Termination Visit | | | | | | | | | | | X |

* If Visit 19 is more then 8 weeks after V13 then the measures from V13 will need to be repeated prior to starting Stage 2 A =First session is 1 day after Exp session B =Approximately 6 hours post MDMA C =At the beginning of the session D =As needed E =Approximately every 60 minutes F = Given on 2nd integrative session only G = For 7 days post Exp. Session, C-SSRS D2 and D7 of calls only, General well being for all 7 days H=CAPS may be videotaped I= Only in subjects with pre-existing tinnitus and/or chronic pain.

## 5.0 Randomization and Blinding

This is a randomized, triple-blind, dose response study with an open-label cross-over segment. For Stage 1, a randomization list will be prepared at the beginning of the study. If needed, subsequent randomization lists will be created to replace subjects who withdraw from the study to ensure that replacement subjects are not added to the end of the initial list. Each subject will be assigned to one of the three dose conditions; 30 mg (low dose), 75 mg (medium dose) or 125 mg (full dose). Twelve evaluable subjects will be assigned to the full dose condition, six evaluable subjects to the 75 mg condition and six evaluable subjects to the 30 mg low dose condition. The study will employ a blinded randomization procedure that will maintain the 2:1:1 ratio while maintaining the blind and ensuring that each subsequent condition assignment is not predicated on the previous assignment.

## 6.0 Sample Size and Power Considerations

This study is a pilot investigation intended to gather preliminary data on the safety and efficacy of MDMA in 24 evaluable veterans, firefighters, or police officers 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 used to collect effect size estimates for statistical power calculations for adequately powered subsequent studies.

## 7.0 Measures

### 7.1 Outcome Measures

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

Global Assessment of Functioning (GAF), total score

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

Post Traumatic Growth Inventory (PTGI), total

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

Pittsburgh Sleep Quality Index (PSQI), total score

NEO Personality Inventory (NEO PI), five factors

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

Long-term Follow-up Questionnaire (LTFU Questionnaire)

### 7.2 Safety Measures

Columbia Suicide Severity Rating Scale (C-SSRS)

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)

### 7.3 Process Measures

Therapist Adherence Criteria

Belief of Condition Assignment

Subject perceptions of experimental sessions

Reactions to Research Participation Questionnaire (RRPQ)

## 8.0 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.

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.

## 8.1 Analysis Populations

*Intent-to-treat (ITT):* all subjects who were randomized

*Per protocol (PP):* all subjects who completed Stage 1, underwent assessment of PTSD symptoms, 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

## 8.2 Handling of Dropouts, Missing Data

Early termination visit data for ITT and Safety variables will be analyzed at the closest scheduled visit. 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.

Subjects who discontinue treatment prior to completing the second experimental session prior to the primary endpoint will be replaced. These subjects will be asked to complete an outcome assessment prior to continuing to the long-term follow-up. These subjects will be included in the ITT population.

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.

## 8.3 Protocol Deviations

All protocol deviations will be included as a categorized listing. Safety and Intent to Treat 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 complete through the primary endpoint and anyone who was enrolled 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 five 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

## 8.4 Pooling of Investigator Centers

All subjects in this study come from one investigational center.

## 8.5 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 3) pre-drug Since Last Visit C-SSRS scores will used as 'baseline.' If a subject was not administered the C-SSRS at preparatory session 2 (visit 3), then 'baseline' scores will be from preparatory session 3 (visit 4).

## 8.6 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 who are randomized and had any treatment exposure, in the Safety Population, in the ITT 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, ITT and PP Populations.

## 8.7 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 ITT and Crossover Populations.

## 8.8 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.

## 8.9 Efficacy Analyses

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

### 8.9.1 Primary Efficacy Analyses

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

The primary efficacy evaluation is the change from baseline to the primary outcome timepoint (visit 13) 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 null hypothesis rejects, pairwise comparisons among the treatment groups will be made with t-tests. If the parametric assumptions for the ANOVA analyses are not met, the analogous nonparametric methods will be used (Kruskall-Wallis, Wilcoxon Rank-Sum).

### 8.9.2 Secondary Efficacy Analyses

#### 8.9.2.1 Secondary Efficacy Analyses at Primary Endpoint

The secondary efficacy analyses will be made with ANOVA comparing change from baseline (visit 1) to the primary outcome timepoint (visit 13) of all the secondary measures. If the parametric assumptions for the ANOVA analyses are not met, the analogous nonparametric methods will be used (Kruskall-Wallis, Wilcoxon Rank-Sum).

Clinician Administered PTSD Scale-4 (CAPS-4) global scores will also be analyzed for effect size with the Cohen's *d* 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.

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

#### 8.9.2.2 Secondary Efficacy Analyses at Secondary Endpoints

Assess 3 vs. 2 experimental MDMA sessions

For the CAPS, PTGI, BDI-II, GAF, PSQI, DES-II, and NEO PI, the absolute changes in the measures from the primary endpoint to end of Stage 1 for the 125 mg group will be compared with t-tests. In the crossover subjects (30 mg and 75 mg group) the absolute

changes in the measures from the secondary endpoint to end of Stage 2 will be compared with t-tests.

Crossover Subject Analyses
Data from subjects assigned to the low and medium dose groups, i.e. 'crossover population,' will be analyzed by within-subject t-tests comparing difference scores from primary endpoint in Stage 1 to secondary endpoint in Stage 2 (Table 3 and 4). The following measures total scores will be analyzed in this fashion: CAPS, PTGI, BDI-II, GAF, PSQI, DES-II, and NEO PI.

Long-term Follow-up
For the CAPS, PTGI, BDI-II, GAF, PSQI, DES-II, and NEO PI, 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 18, 125 mg) or long-term follow-up compared to End of Stage 2 (visit 33, 30 and 75 mg) will be compared with within-subject t-tests.

### 8.9.3 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 will be an indirect measure of clinical significance. Descriptive statistics will be computed and displayed by Stage 1 conditions.

- The percentage of subjects who no longer meet PTSD diagnostic criteria at the primary endpoint will be an indirect measure of clinical significance. Descriptive statistics will be computed and displayed by Stage 1 conditions.

- CAPS-4 Subscale Scores (B, C, D, F) at the primary endpoint 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 conditions.

- Distributional characteristics will be examined for outliers and extreme values and, if either is evident. If outliers are found in primary or secondary outcome measures, the sponsor will perform analyses with and without the outlying data

#### 8.9.3.1 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 condition to actual MDMA dose received in each blinded session, the frequency of correct guesses will be calculated and depicted by dose condition and study role (subject, therapist, or independent rater).

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 125 mg group, within-subjects t-tests will be performed on subject's perceptions at Stage 1 primary and secondary endpoints. The same analysis will be performed for 30 mg and 75 mg groups, but data will be from Stage 2 primary and secondary endpoint.

Reactions to Research Participation Questionnaire (RRPQ)
Frequency of response will be tabulated for 'reasons for participation' across Stage 1 conditions. 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.

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.

### 8.9.4 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 those existing AEs 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 adverse event mapped to the same preferred term, that adverse event will be reported only once using the highest severity and closest relationship to study drug. In separate columns, the overall frequency of AE's will be reported. Subject incidence of adverse events will be displayed by treatment group and by system organ class. Adverse events will also be summarized by severity and relationship to study drug. Subject incidence of serious adverse events by treatment group will also be displayed. In addition to the listing of all adverse events, a listing of serious adverse events and a listing of adverse events leading to discontinuation of study drug will be included.

Summary tables of frequency listings of expected adverse events (Spontaneously Reported Reactions) mapped to preferred terms will be displayed during and after each experimental session by condition.

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 [3]. 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 treatment group and time period. P-values will be calculated using the chi-squared test for overall treatment group differences and Fisher's exact test will be used for pairwise testing. Compare lifetime serious suicidal ideation and positive behavior frequencies to cumulative frequencies anytime during the study until end of stage 1 and stage 2 using chi-squared test for overall treatment group differences and Fisher's exact test for pairwise testing.

Subjective Units of Distress (SUD)

Descriptive statistics for SUD scores will be calculated by 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 condition. T-tests will be performed 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 conditions, with p set at 0.05. If the only scores available are for subjects in a single condition, then a paired t-test will be performed comparing baseline and primary endpoint Changes in Tinnitus and/or Pain visual analog scale scores, with p set at 0.05.

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. For experimental sessions, mean peak heart rate, blood pressure, and body temperature will be analyzed by condition with ANOVA, with t-tests for pairwise comparisons. 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. A within-subjects t-tests for pre- and post-drug endpoints will be conducted for each session for heart rate, blood pressure, and body temperature.

## 8.10 Timing of Analyses

The primary efficacy analysis will be conducted after all subjects complete Stage 2, but before all long-term follow-up data has 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. The final analysis of secondary endpoints will include only data not analyzed in the primary efficacy analysis, i.e. data will not be analyzed twice.

## 9.0 References

1. Mithoefer, M.C., et al., *The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study.* J Psychopharmacol, 2011. **25**(4): p. 439-52.

2. Mithoefer, M.C., et al., *Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study.* J Psychopharmacol, 2013. **27**(1): p. 28-39.
3. 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.