Internal Approval Page

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This document was subject to review. The information it contains is consistent with:

- The current version of the Investigator's Brochure
- The moral, ethical and scientific principles governing clinical research as set out in the Good Clinical Practice guidelines

The investigator will be supplied with details of any significant or new findings, including adverse events.

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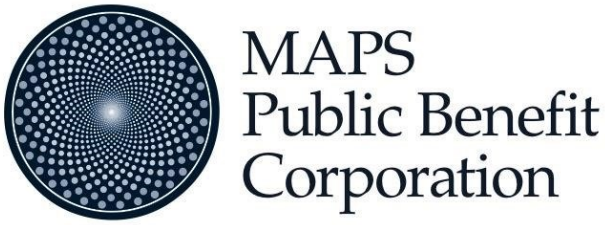

MDA-1 Statistical Analysis Plan

Version 1: 7 August 2017

CORPORATION	MAPS Public Benefit Corporation (MPBC) 1115 Mission Street Santa Cruz, CA 95060
CORPORATION DESIGNEE	Amy Emerson Executive Director and Director of Clinical Research
USE	In conjunction with relevant FDA guidance
STUDY TITLE	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Illness
LATEST PROTOCOL	Amendment 5 Version 1, August 14, 2013
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List of Abbreviations

AE	Adverse Event
BDI-II	Beck Depression Inventory-II
BPI-S	Brief Pain Inventory-Short Form
BT	Body Temperature
C-SSRS	Columbia Suicide Severity Rating Scale
DAP	Death Attitudes Profile
DBP	Diastolic Blood Pressure
ES	Effect Size
FACIT	Functional Assessment of Chronic Illness Therapy Scale
FFMQ	Five-Facet Mindfulness Questionnaire
GAF	Global Assessment of Functioning
GWB	General Well-being
HR	Heart Rate
ITT	Intent To Treat
MADRS	Montgomery-Asberg Depression Rating Scale
MAPS	Multidisciplinary Association for Psychedelic Studies
PP	Per Protocol
PPQ	Psychological Process Questionnaire
PSQI	Pittsburgh Sleep Quality Index
PTGI	Post Traumatic Growth Inventory
PTGI-C	Posttraumatic Growth Inventory—Caregiver Form
SBP	Systolic Blood Pressure
SCS	Self-Compassion Scale
SOCQ	States of Consciousness Questionnaire
STAI	State-Trait Anxiety Inventory

1.0 Definitions of Terms

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

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

2.0 Introduction

This document contains a Statistical Analysis Plan for the study, "A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Illness"

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval for the prescription use of 3,4methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in persons with anxiety associated with a life-threatening illness.

This is an initial pilot study to assess the efficacy of MDMA for this indication, following promising results from MAPS-sponsored studies of MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD).

This study, MDA-1, will examine the safety and efficacy of MDMA-assisted psychotherapy in 18 individuals with anxiety associated with a life-threatening illness, which may be either current or in remission with the possibility of recurrence, and will seek to enroll roughly equal numbers of men and women. This study will include those with moderate to severe anxiety, as measured by the Trait subscale of the Spielberger State-Trait Anxiety Inventory. Full dose and placebo MDMA will be assessed in Stage 1, as well as the benefit of three vs. two full dose sessions. Subjects who received the 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.

This pilot study is an early investigation in this indication. As a result, the sponsor will perform tests on all statistical comparisons as exploratory and hypothesis generating without correcting for multiple comparisons.

3.0 Study Objectives

3.1 Primary Objective

The primary objective is to assess changes in anxiety symptoms via the Trait subscale of the State-Trait Anxiety Inventory (STAI) in subjects randomized to study arms (MDMA and placebo) at baseline and the primary endpoint, one month after the second experimental session.

3.2 Secondary Objectives

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

- Assess changes in self-reported State Anxiety symptoms as measured with the State-Trait Anxiety Inventory—State subscale (STAI-State) from Baseline to the Primary Endpoint.

- Assess changes in self-reported depression symptoms with the Beck Depression Inventory- II (BDI-II) from Baseline to the Primary Endpoint.
- Assess changes in clinician ratings of depression symptoms with the Montgomery Asberg Depression Rating Scale (MADRS) from Baseline to the Primary Endpoint.
- Assess changes in quality of life with Functional Assessment of Chronic Illness Therapy Scale (FACIT-Sp) from Baseline to the Primary Endpoint.
- Assess changes in global functioning with the Global Assessment of Functionality (GAF) from Baseline and the Primary Endpoint.
- Assess changes in self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) from Baseline to the Primary Endpoint.
- Assess changes in subjects' attitudes toward death with the Death Attitudes Profile (DAP) from Baseline to the Primary Endpoint.
- Assess personal growth with the Post-Traumatic Growth Inventory (PTGI) from Baseline to the Primary Endpoint.
- Assess caregiver perceptions of subjects' personal growth with the Post- Traumatic Growth Inventory—Caregiver Form (PTGI-C) from Baseline to the Primary Endpoint.
- Assess changes in self-oriented compassion with the Self-Compassion Scale (SCS) from Baseline to the Primary Endpoint.
- Assess changes in self-reported mindfulness with the Five-Facet Mindfulness Questionnaire (FFMQ) from Baseline to the Primary Endpoint.
- Explore the effects of each experimental session with active dose MDMA or placebo upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Explore the effects of each experimental session upon self-reported cognitive and emotional processing via the Psychological Process Questionnaire (PPQ).
- Assess the effect of the third experimental session using a within-subject comparison of the Primary/Secondary Endpoint to 1-month follow-up assessment in active dose subjects using STAI-Trait, STAI-State, MADRS, BDI-II, DAP, GAF, FFMQ, PTGI, PSQI, PTGI-C, SCS, and FACIT.
- Conduct a within-subject analysis comparing Stage 1 and Stage 2 in placebo subjects using STAI-Trait, STAI-State, MADRS, BDI-II, DAP, GAF, FFMQ, PTGI, PTGI-C, PSQI, SCS, and FACIT at the Primary and Secondary Endpoints.
- Assess durability of changes in outcome measures using STAI-Trait, STAI-State, MADRS, BDI-II, DAP, GAF, FFMQ, PTGI, PTGI-C, PSQI, SCS, and FACIT at the 6month and 12-month follow-up visits.
- Assess qualitative reports of subjects' experiences in the study via a semi- structured interview at the 1-month follow-up assessment.
- Assess observations of the subject's overall state of being from up to three observers using the Observer Rating Form (ORF) at Baseline, the Primary Endpoint, and the 6- and 12-month follow-up visits.
- Assess the ability of the Clinical Investigator(s) (CI) and subjects to accurately guess condition assignment in Stage 1.

3.3 Safety Objectives

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during visits prior to experimental sessions, twice during experimental sessions, and several times after each experimental session, with comparisons made between subjects in each condition.
- Subjective Units of Distress (SUD) and vital signs including blood pressure, heart rate, and temperature will be measured during each experimental session. Vital signs will be compared between subjects in each condition.
- Changes to pre-existing chronic pain symptoms, when applicable, will be collected using the Brief Pain Inventory—Short Form (BPI-S) at Baseline and throughout the study, with comparisons made for Primary Endpoint, end of Stage 1 or Stage 2 and 6- and 12-month follow up.
- Serious adverse events (SAEs), adverse events, and spontaneously reported reactions will be collected during the study according to Section 8.5 of the protocol.

4.0 Study Design

This is a randomized, double-blind, placebo-controlled pilot study that will examine the safety and efficacy of MDMA-assisted psychotherapy in subjects diagnosed with anxiety associated with a life-threatening cancer or non-dementing neurological illness, which may be ongoing or in remission but with the possibility of recurrence. Stage 1 will include two blinded and one open-label MDMA-assisted psychotherapy sessions scheduled two to four weeks apart with a male/female co-therapist team. Therapy teams will consist of varying combinations of the Principal Investigator, experienced co- therapists, and intern co-therapists. Subjects will be treated by the same therapy team throughout their participation in the study. There will also be a moderate course of preparatory sessions and integrative sessions, as described in the Time and Events Table.

Upon enrollment, subjects will be randomly assigned to receive either placebo (n=5) or active dose (n=13) MDMA. In Stage 1, subjects will meet with their therapist team for three preparatory sessions and two blinded experimental sessions of MDMA-assisted psychotherapy. After each experimental session, subjects will stay overnight at the site and complete an integrative session the next day, followed by daily telephone calls for the next seven days and two additional integrative sessions. One month after the second experimental session, the Primary Endpoint assessment will take place, after which the blind will be broken. All subjects who received the active dose will then receive a third open-label experimental session with active dose MDMA. Subjects who receive the placebo will be offered the option to continue to the open-label Stage 2, unless they meet any exclusion criteria for study participation. In Stage 2, subjects will receive active dose MDMA in three experimental sessions that will otherwise follow the same sequence of events after a single preparatory session. (See Time and Events Table).

A blinded Independent Rater will administer the MADRS and the GAF; all other outcome measures will be collected via subjects' self-report or via report provided by a caregiver or observer.

Anxiety symptoms will be assessed in all subjects throughout Stage 1, and anxiety symptoms will be assessed throughout Stage 2 for subjects continuing on to Stage 2. All subjects will complete a follow-up occurring one month after their third experimental session in Stage 1 for active dose subjects, and one month after their third experimental session in Stage 2 for subjects who received placebo in Stage 1. In addition, all subjects will complete visits six months and then 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).
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 1: Stage 1 Blinded Drug Doses

Group	Number of Subjects	Initial Dose	Supplemental Dose	Min-Max Cumulative Dose
Placebo	5	0 mg	0 mg	0 mg
Full Dose	13	125 mg	62.5 mg	125-187.5 mg

Table 2: Stage 2 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose
1, 2, & 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

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

Table 3.Stage 1 Time& Events	Preparatory		Experimental Session 1		Experimental Session 2			Experimental Session 3		Follow-Up
Visit #	Pre-Study	V 1,2,3	V4	V 5,6,7	V8	V 9,10,11	V12	V13	V 14,15,16	V17
Type of Visit	Screening may take place over more than one day	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 V4	Up to 5 weeks post V1	Before V8 [A]	2-4 weeks post V4	Before V12[A]	1 month +/- 1 week post V8	3-4 weeks post V8 [N]	Before V17 [A, N]	May happen over > 1 day. 1 mo. +/- 1 week post V13 [N]
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Phys. Exam (BP, Pulse, Temp)	✓									
Brief Neurological Exam	✓									
ECG	✓									
SCID-RV	✓									
Clinical Lab Tests, w/ HIV, HCV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication Taper (if applicable)	✓									
Study Enrollment after meeting I/E		✓[G]								
Record to Audio/Video		✓	✓	✓	✓	✓	✓	✓	✓	✓
General Well-Being		✓	✓	✓	✓	✓		✓	✓	
Drug Screen	✓		✓		✓			✓		
Pregnancy Screen (if applicable)	✓		✓		✓			✓		
Complete Randomization Procedure			✓[B]							
STAI-Trait	✓						✓			✓
STAI-State	✓	✓[I]					✓			✓
BDI-II	✓			✓[L]			✓			✓
BPI-Short		✓[I]		✓[K]		✓[K]	✓		✓[K]	✓
GAF, MADRS		✓					✓			✓
DAP, PTGI, PTGI-C PSQI		✓[G]					✓			✓
FFMQ, SCS		✓[H]					✓			✓

FACIT		✓I					✓			✓
ORF	✓						✓			
C-SSRS	✓	✓	✓C, D, E	✓J, M	✓C, D, E	✓J,M	✓	✓C, D, E	✓J,M	✓
Administer IP Drug + Therapy, SOCQ, PPQ			✓		✓			✓		
Monitoring of BP, Pulse and Temp.			✓		✓			✓		
SUD			✓F, E		✓F, E			✓F, E		
Beliefs of Condition Assignment				✓K		✓K			✓K	
Overnight Stay			✓		✓			✓		
Integrative Therapy Session				✓		✓			✓	
7 days Integrative Telephone Contact				✓J		✓J			✓J	
AEs Requiring Medical Attention			✓	✓	✓	✓	✓	✓	✓	✓
Spont. Reported Reactions and all AEs			✓	✓	✓	✓		✓	✓	
AEs of psychiatric status or withdrawal		✓	✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Issue Memory Aid Card										✓
Semi-Structured Interview										✓
Unblinding J							✓			

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 90 minutes G =Given on 1st preparatory session (V2) H= Given on 2nd preparatory session (V1) I= Given on 3rd preparatory session (V3) J =For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well-being for all 7 days. K= On the day of the 1st integrative session following the Exp. Session L=On the third integrative session after the first experimental session only. M= Given at all three integrative sessions

Table 4. Time & 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	2-4 weeks post V19	Between V23 and V27	1 month +/- 1 week post V23	3-4 weeks post V23	Between V28 and V32	1 month +/- 1 week post V28	6 months AND 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)		✓		✓			✓			
STAI-Trait, MADRS	Use V12*					✓H			✓	✓
STAI-State, GAF, DAP, PTGI, PTGI-C PSQI, FFMQ, SCS, FACIT	Use V12*					✓			✓	✓
BDI-II	Use V12*		✓J			✓			✓	✓
BPI-Short	Use V12*		✓I		✓I	✓		✓I	✓	
ORF						✓				✓
C-SSRS	✓	✓B,C,D	✓G,K	✓B,C,D	✓G,K	✓	✓B,C,D	✓G,K	✓	✓
Administer Drug + Therapy		✓		✓			✓			
Monitoring of BP, Pulse, and Temp.		✓		✓			✓			
SUD		✓D,E		✓D,E			✓D,E			
Overnight Stay, SOCQ, PPQ		✓		✓			✓			
Integrative Therapy Session			✓A		✓A			✓A		
Seven Days Telephone Contact			✓		✓			✓		
AEs Requiring Medical Attention	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Spont. Reported Reactions and all AEs		✓	✓F	✓	✓F		✓	✓F		
AEs of psychiatric status or withdrawal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Complete Stage 2 go to follow-up									✓		
Issue Memory Aid Card									✓		
Semi-Structured Interview									✓		
Follow-up Questionnaire											✓L
Termination Visit											✓L

* If Visit 18 is more than 30 days 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 90 minutes; F = Reactions collected for seven days post experimental session; G = Day 2 and Day 7 phone calls only; H = 2 weeks after the second experimental session but before the third experimental session; I = On the day of the first integrative session following the Exp. Session; J=At the third integrative session following the first experimental session only; K=At all three integrative sessions; L=At the 12-month follow-up visit only.

5.0 Randomization and Blinding

Each subject will be assigned to one of the two dose conditions: placebo or 125 mg (full dose). Thirteen evaluable subjects will be assigned to the full dose condition, and five to the placebo condition. The study will employ a blinded list-based randomization procedure that will maintain the 13:5 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 18 evaluable individuals with anxiety related to a life-threatening illness. 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

- State-Trait Anxiety Inventory (STAI), Trait Subscale
- State-Trait Anxiety Inventory (STAI), State Subscale
- Global Assessment of Functioning (GAF), total score
- Beck Depression Inventory-II (BDI-II), total score
- Post Traumatic Growth Inventory (PTGI), total
- Post Traumatic Growth Inventory—Caregiver Form (PTGI-C), total score
- Montgomery-Asberg Depression Rating Scale (MADRS), total score
- Pittsburgh Sleep Quality Index (PSQI), total score
- Observer Rating Form (ORF)

- Functional Assessment of Chronic Illness Therapy Scale (FACIT-Sp), total and composite scores
- Death Attitudes Profile (DAP), composite scores
- Five-Facet Mindfulness Questionnaire (FFMQ), composite scores
- Self-compassion Scale (SCS)
- 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)
- Brief Pain Inventory—Short Form (BPI-S)
- 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

- Belief of Treatment Group Assignment
- States of Consciousness Questionnaire (SOCQ), total and composite scores
- Psychological Process Questionnaire (PPQ), total and composite scores

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. 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 anxiety 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. 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. If subjects repeat a measure because the next visit is out of the allotted time window, data from the most recent visit will be included in analyses.

8.2.1 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 CSSRS, pre-enrollment scores will be used as a measure of 'lifetime' suicidal ideation and behavior, and preparatory sessions and pre-drug experimental session 1 C-SSRS will be used as 'baseline.'

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

State-Trait Anxiety Inventory, Trait Subscale

The primary efficacy evaluation is the change from baseline to the primary outcome timepoint (visit 13) in the STAI-Trait subscale (difference score). The primary efficacy comparison on difference scores will be made with an independent sample t-test at an alpha level of 0.05. If the parametric assumptions for the independent samples t-test analyses are not met, the analogous nonparametric methods will be used (Wilcoxon Rank-Sum test).

8.9.2 Secondary Efficacy Analyses

8.9.2.1 Secondary Efficacy Analyses at Primary Endpoint

The secondary efficacy analyses will be made with independent samples t-tests at an alpha level of 0.05 comparing change from baseline (visit 1) to the primary outcome timepoint (visit 13) for the following secondary measures. If the parametric assumptions for the independent samples t-test analyses are not met, the analogous nonparametric methods will be used (Wilcoxon Rank-Sum test).

State-Trait Anxiety Inventory (STAI) Trait subscale sores will also be analyzed for effect size with the Cohen's *d* analysis.

State-Trait Anxiety Inventory (STAI) State subscale scores will be analyzed in the same manner as the STAI-Trait scale primary analysis.

Montgomery-Asberg Depression Rating Scale (MADRS) total will be analyzed in the same manner as the STAI-Trait scale primary analysis.

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

Functional Assessment of Chronic Illness Therapy Scale (FACIT-Sp) factor scores will be analyzed in the same manner as the STAI-Trait scale primary analysis.

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

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

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

Death Attitudes Profile (DAP) factor scores will be analyzed in the same manner as the STAI-Trait scale primary analysis.

Five-Facet Mindfulness Questionnaire (FFMQ) factor scores will be analyzed in the same manner as the STAI-Trait scale primary analysis.

Posttraumatic Growth Inventory—Caregiver Form (PTGI-C) total will be analyzed in the same manner as the STAI-Trait scale primary analysis.

Self-Compassion Scale (SCS) total will be analyzed in the same manner as the STAI-Trait scale primary analysis.

Observer Rating Form (ORF) subscale and total scores will be analyzed in the same manner as the STAI-Trait scale primary analysis.

8.9.2.2 Secondary Efficacy Analyses at Secondary Endpoints

Assess 3 vs. 2 experimental MDMA Sessions
For the STAI-Trait, STAI-State, PTGI, PTGI-C, BDI-II, GAF, PSQI, FACIT-Sp, MADRS, FFMQ, DAP, and SCS, 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 (placebo 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 placebo group, 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. The following measures total scores will be analyzed in this fashion: STAI-Trait, STAI-State, PTGI, PTGI-C, BDI-II, GAF, PSQI, FACIT-Sp, MADRS, FFMQ, DAP, and SCS.

Six- and Twelve-month Follow-up
For the STAI-Trait, STAI-State, PTGI, PTGI-C, BDI-II, GAF, PSQI, FACIT-Sp, MADRS, FFMQ, DAP, and SCS, the absolute changes in the measures from baseline to

the 6- and 12-month follow-up visit will be compared with t-tests. The absolute changes in the measures from follow-up visits to End of Stage 1 (visit 18, 125 mg) or follow-up visits compared to End of Stage 2 (visit 33, placebo) will be compared with within-subject t-tests.

8.9.3 Exploratory Analyses

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

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 average SOCQ scores for blinded experimental sessions will be compared between treatment groups using independent samples t-tests at an alpha level of 0.05. The data will be explored for effects on domain scores in the SOCQ. If MDMA significantly reduces trait anxiety when compared with placebo, the sponsor will run a two-tailed Pearson's correlation on STAI-Trait and SOCQ total scores to determine whether experiencing a non-ordinary state of consciousness or any facet of this state is associated with a change in anxiety symptoms.

Psychological Process Questionnaire (PPQ)
Descriptive statistics will be computed for PPQ scores completed after each MDMA-assisted psychotherapy session, and average PPQ scores for blinded experimental sessions will be compared between treatment groups using independent samples t-tests at an alpha level of 0.05. If MDMA significantly reduces trait anxiety when compared with placebo, the sponsor will run a Pearson's correlation on STAI-Trait and PPQ total scores to determine whether experiencing a non-ordinary state of consciousness or any facet of this state is associated with a change in anxiety symptoms.

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 Treatment Group Assignment
In order to compare the therapists', independent raters', and subjects' belief of treatment assignment 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).

Qualitative Interviews

Qualitative interviews conducted by a researcher who is part of the study team during the follow-up visit one month after the final experimental session 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.

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 t-tests. 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.

Brief Pain Inventory-Short Form (BPI-S)
Descriptive statistics for BPI responses will be calculated by treatment group and time period with counts and percentages. Within-subjects t-tests will compare scores at baseline to scores at Primary Endpoint, End of Stage 1 or 2, 6-month follow-up, and 12month follow-up.

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 {+/-}3,4methylenedioxymethamphetamine-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 3,4methylenedioxymethamphetamine-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.