MP-9 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, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-assisted Psychotherapy in People with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
LATEST PROTOCOL	Amendment 3 Version 1, March 30, 2015
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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
ES	Effect Size
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
PDS	PTSD Diagnostic Scale
PP	Per Protocol
PTSD	Posttraumatic Stress Disorder
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized Controlled Trial
RRPQ	Reactions to Research Participation Questionnaire
SBP	Systolic Blood Pressure
SUD	Subjective Units of Distress

2.0 Introduction

This document presents a Statistical Analysis Plan (SAP) for MAPS study protocol MP-9, a Phase 2 pilot clinical trial designed to evaluate the safety and effect of MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD.

The statistical plan described hereafter is an *a priori* plan based on the statistical analysis plans included in the study protocol. This SAP will be finalized prior to any unblinded or inferential or descriptive analyses of data pertaining to the MAPS MP-9 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. An active dose of MDMA (125 mg) and a comparator dose (25 mg) will be assessed in two Stage 1 sessions. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over and take part in a second study segment, referred to as Stage 2, with two open-label experimental sessions. Co-therapist teams of psychotherapists will conduct the study.

This study is designed to obtain estimates of effect size for effect and collection of safety data. The data will be analyzed with ongoing Phase 2 dose response studies in a meta-analysis. 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 participants receiving the full dose of MDMA and the active placebo dose as measured via CAPS score at baseline and the end of Stage 1

4.2 Secondary Objectives

- Assess changes in self-reported PTSD symptoms in participants receiving the full dose of MDMA and the active placebo dose as measured via PDS score at baseline, during the third integrative session after each experimental session and at the end of Stage 1.
- Assess depression symptoms via the Beck Depression Inventory- II (BDI-II) at baseline and the end of Stage 1.
- Assess quality of life via the Global Assessment of Functionality (GAF) at baseline and the end of Stage 1.

- Assess self-reported sleep quality via the Pittsburgh Sleep Quality Index (PSQI) at baseline and the end of Stage 1.
- Assess PTSD symptoms via CAPS, depression symptoms via BDI-II, quality of life via GAF and sleep quality with PSQI at the end of Stage 2 in all participants enrolled in Stage 2.
- Assess long-term effects symptoms of PTSD, depression and global function via CAPS, PDS, BDI-II and GAF one year after the final MDMA-assisted psychotherapy session for each participant.
- Assess changes in PTSD symptoms via PDS during the third integrative session after each Stage 2 experimental session and at the end of Stage 2.

4.3 Safety Objectives

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

- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during 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) scores and vital signs including blood pressure, heart rate and temperature will be measured during each experimental session, and results will be compared between groups.
- Serious adverse events, adverse events and spontaneously reported adverse events ("reactions") will be collected during the study according to Section 8.5.

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 will examine the safety and effect of MDMA-assisted psychotherapy in subjects diagnosed with chronic, treatment-resistant PTSD of at least six-months duration. The open-label lead-in, Stage 1 and Stage 2 will follow the same basic sequence of events and methods. The schedule will include two MDMA-assisted psychotherapy sessions scheduled approximately one month apart with a male/female co-therapist team. There will be multiple male/female co-therapist teams, but subjects will remain with only one team for the entirety of the study. The first two teams will complete treatment of one of the two open-label lead-in subjects for training purposes. 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 experimental psychotherapy sessions assisted by either active placebo MDMA (3 subjects) or full dose MDMA (5 subjects). Subjects who receive the active 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 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, if applicable. The blind will be broken for all subjects in Stage 1 after completing this assessment. 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

Number of Subjects	Condition	Blind?	Initial Dose	Supplemental Dose	Cumulative Dose
2	Lead-jn	Open Label	125 mg	62.5 mg	187.5 mg
3	Active Placebo Dose	Blinded	25 mg	12.5 mg	37.5 mg
5	Full Dose	Blinded	125 mg	62.5 mg	187.5 mg
3 or less	Stage 2	Open Label	125 mg	62.5 mg	187.5 mg

Table 2. Time & Events MP9 Stage 1	Screen/Baseline	Preparatory	Experimental Session 1		Experimental Session 2		End of Stage 1
Visit #	Prior to Enrollment	V1, 2, 3	V4	V5, 6, 7	V8	V9, 10, 11	V12
Type of Visit	Baseline Screening may take place over more than one day up to one month prior to Visit 1	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Follow-Up & Outcome
Visit Timing or Study day or Window		Approx. 1 week apart	3-5 weeks post V1	Approx. 1 week apart [A]	3-5 weeks post V4	Approx. 1 week apart [A]	May happen over more then 1 day. 2 months post V8
Informed Consent	X						
Medical/Psychiatric History	X						
General Physical Exam, ECG	X						
Brief Neurological Exam	X						
SCID	X						
Clinical Lab Tests, w/ HIV test	X						
Collect Concomitant Medication		X	X	X	X	X	X
Medication Taper (if applicable)		X					
Drug Screen	X		X		X		
Pregnancy Screen (if applicable)	X		X		X		
CAPS, GAF, BDI –II, PSQI (with Ind. Rater)	X						X
Study Enrollment after meeting I/E		X [B]					
Record to Audio/Video		X	X	X	X	X	
General Well-Being		X	X [D]	X	X [D]	X	X
Obtain Container Assignment			X [C]		X [C]		
C-SSRS	X	X [H]	X [D, E, F]	X [J]	X [D, E, F]	X [J]	X
Administer IP Drug + Therapy			X		X		
Monitoring of BP, Pulse and Temp.			X		X		
SUD			X [E, G]		X [E, G]		
Beliefs of Condition Assignment				X [I]		X [I]	
Overnight Stay			X		X		
PDS	X			X [N]		X [N]	X
Integrative Therapy Session				X		X	
7 days Integrative Telephone Contact				X [J]		X [J]	
AEs Requiring Medical Attention			X	X	X	X	X
Spont. Reactions and all AEs			X [K]	X [K]	X [K]	X [K]	
AEs related to changes in psychiatric status or withdrawal		X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X
Unblinding							X [L]
RRPQ							X [M]
Issue Memory Aid Card							X [M]

A =First Integrative session is 1 day after Exp. session B =Only on Visit 1 C = At least 24 hrs prior to exp. session D =Approximately 6 hours post MDMA E =At the beginning of the session F =As needed G =Approximately every 60 minutes H =Given on 2nd preparatory session only (V2) I= At 1st integrative visit after each Exp. Session for subjects & therapists and at V12 for the independent rater J = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days K= Spontaneously reported reactions will be collected on the day of MDMA administration and for seven days after each Exp. Session. L= Determine after completion: Go on to Long-term follow up or Stage 2 M= Only for subjects not going to Stage 2 N= Subjects will complete PDS on third integrative session only

Table 3. Time & Events MP9 Stage 2	**Preparatory**	**Experimental Session 1**		**Experimental Session 2**		**End of Stage 2**	**Long Term Follow up after Stage 1 or Stage 2**	**Long Term Follow-Up**
Visit #	V13*	V14	V 15, 16, 17	V18	V 19, 20, 21	V22		1 Year Follow-up
Type of Visit	Preparatory Session	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Follow-Up & Outcome		Follow-Up & Outcome
Visit Timing or Study day or Window	Within 1 month of V12*	1 week post V13	Approx. 1 week apart [A]	3-5 weeks post V14	Approx. 1 week apart [A]	May happen over more then 1 day. 2 months post V17		May happen over more then 1 day. One Year After V8 or V17
Confirm Informed Consent	X							
Confirm Inclusion/Exclusion	X							
Entry into Stage 2	X							
Collect Concomitant Medication	X	X	X	X	X	X		X
Record to Audio/Video	X	X	X	X	X			
General Well-Being	X	X[B]	X	X[B]	X	X		X
Drug Screen		X		X				
Pregnancy Screen (if applicable)		X		X				
CAPS, GAF, PSQI, BDI-II (with Ind. Rater)	Use V12*					X		X
C-SSRS	X	X[B, C, D]	X	X[B, C, D]	X	X		X
Administer IP Drug + Therapy		X		X				
Monitoring of BP, Pulse and Temp.		X		X				
SUD		X[C, E]		X[C, E]				
Overnight Stay		X		X				
PDS	Use V12*		X[H]		X[H]	X		X
Integrative Therapy Session			X		X			
7 days Integrative Telephone Contact			X[F]		X[F]			
AEs Requiring Medical Attention	X	X	X	X	X	X		
Spont. Reactions and all AEs		X[G]	X[G]	X[G]	X[G]			
AEs related to changes in psychiatric status or withdrawal	X	X	X	X	X	X		X
Serious Adverse Events	X	X	X	X	X	X		X
RRPQ						X		
Issue Memory Aid Card						X		
Follow up Questionnaire								X
Termination Visit								X

* Re-baseline if Visit 13 is more than 1 month from V12, then the measures from V12 will need to be repeated prior to starting Stage 2.
A = First Integrative 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 = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days G= Spontaneously reported reactions will be collected on the day of MDMA administration and for seven days after each Exp. Session. H = Subjects will complete PDS on third integrative session only

6.0 Randomization and Blinding

In total, ten subjects will be enrolled into the study. The first two subjects will be enrolled in the open-label lead-in and assigned to the full dose condition. The subsequent eight subjects will be enrolled in the randomized Stage 1. The randomized portion of the study will be blinded and there will be a 5/3 ratio between subjects in the Full Dose and Active Placebo conditions. Subjects will be assigned subject numbers, and subjects will be randomized in a blinded fashion.

7.0 Sample Size and Power Considerations

This study is a pilot investigation intended to gather preliminary data on the safety and effect of MDMA-assisted psychotherapy in ten 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. Any significance testing will be considered exploratory.

8.0 Measures

8.1 Outcome Measures

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

PTSD Diagnostic Scale (PDS), total score

Global Assessment of Functioning (GAF), total score

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

Pittsburgh Sleep Quality Index (PSQI), total score

8.2 Safety Measures

Columbia Suicide Severity Rating Scale (C-SSRS)

Subjective Units of Distress (SUD)

General Well-being (GWB)

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

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 and analyzed using chi square analysis. Although the protocol plan specifies parametric t-tests and ANOVAs, the small group sizes (n=3 and n=5) make it a challenge to statistically assess the effectiveness of the treatment. Therefore, this statistical analysis plan acts to amend the data analysis plan in the protocol.

Clinical data will be presented in tabular format. Data not subject to analysis according to this plan will not appear in any tables or graphs, but will be included in the data listings. Analyses will be carried out with SAS Version 9.3 or higher. Selected results may be presented graphically using standard graphical software.

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

9.1 Analysis Populations

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

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

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

Safety: all subjects who receive any study treatment

9.2 Handling of Dropouts, Missing Data

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

Early termination visit data 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 signing informed consent will be summarized descriptively for each treatment group. Concomitant medications will be summarized similarly. Prior and concomitant medications will be summarized for the Safety Population. Psychiatric medications will be coded to common drug classes and terms.

9.9 Effect Analyses

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

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

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

X = treatment means

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

9.9.1 Primary Effect Analyses

Clinician Administered PTSD Scale-4 (CAPS-4)

The primary effect evaluation is the change from baseline to the end of stage 1 outcome timepoint (visit 12) in the CAPS-4 Global Severity score of PTSD (difference score).

9.9.2 Secondary Effect Analyses

The secondary effect analyses will be made comparing change from baseline (Baseline) to the end of stage 1 outcome timepoint (visit 12) of all the secondary measures except the PDS, following the same methodology used for the primary endpoint.

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

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

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

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

9.9.2.1 Secondary Effect Analyses 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.

Long-term Follow-up
For the CAPS, PDS, BDI-II, GAF, and PSQI, the absolute changes in the measures from baseline to the long-term follow-up visit (one year post final experimental year) will be compared. The absolute changes in the 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 compared.

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 end of stage 1 endpoint (visit 12) will be an indirect measure of clinical significance. Descriptive statistics will be computed and displayed by Stage 1 treatment groups.

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

PTSD Diagnostic Scale (PDS)
PDS total scores at baseline, after the third integrative session (Visit 7), the sixth integrative session (Visit 11) and at the end of stage 1 will be examined. Results will be used to examine the effects of each experimental session on self-reported PTSD symptom severity.

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

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

Primary and Secondary Effect Analyses Including 2 Lead-in Subjects
Analyses detailed in Sections 9.9, 9.9.1 and 9.9.2 will be conducted in the same manner with inclusion of the 2 open label, lead-in subjects in the 125 mg treatment group.

9.9.3.1 Process Measures

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 actual MDMA dose received in each blinded session, the number and frequency of correct guesses will be calculated and depicted by dose group and study role (subject and each therapist).

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.

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 by stage will also be displayed. In addition to the listing of all AEs, a listing of SAEs and a listing of AEs leading to discontinuation of study drug will be included.

Summary tables of frequency listings of commonly reported AEs (Spontaneously Reported Reactions) mapped to preferred terms will be displayed during and after each experimental session by Stage 1 treatment group.

Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and behavior will be summarized according to suggestions made in the Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide [2]. A positive response for suicidal ideation is counted when a subject answers "yes" to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS, i.e. a score > 0 for suicidal ideation score. Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a subject answers "yes" to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS, i.e. a score > 0 for suicidal behavior score. The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated by Stage I treatment group and time period. Compare lifetime serious suicidal ideation and positive behavior frequencies to cumulative frequencies anytime during the study until end of Stage 1 and Stage2.

Subjective Units of Distress (SUD)

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

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.

9.10 Timing of Analyses

The primary effect analysis will be conducted after all subjects complete Stage 2, but before all long-term follow-up data have been collected. Subsequent analyses on this data set will not be conducted after initial analyses are performed, unless for further exploratory post-hoc analyses. Changes to protocol will not occur after primary analysis.

10.0 Statistical Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.3 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

11.0 References

References

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

2. Nilsson, M.E., et al., *Columbia Suicide Severity Rating Scale Scoring and Data Analysis Guide*, in *CSSRS Scoring Version 2.0*. 2013: http://www.cssrs.columbia.edu/documents/ScoringandDataAnalysisGuide_Feb2013.pdf. p. 1-13.