Data Analysis Plan

Study Protocol
3,4-methylenedioxymethamphetamine-assisted psychotherapy in Twelve Patients with Treatment-Resistant Posttraumatic Stress Disorder (PTSD.

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Sponsor:

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1.0 Definitions

Categorical data: This refers to discrete (indivisible) variables, such as gender or ethnicity. These data will be presented as total numbers of each category as needed to describe the sample.
Descriptive data: This includes mean, median, standard deviation, minimum and maximum of numerical data used as needed to describe the sample.
Difference scores: These 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: A type of analysis used to assess therapeutic effects or benefits.
Exploratory analyses: An inferential or descriptive analysis of the data to determine trends that might lead to hypotheses for further study.
Frequency listing: A tabular listing of numbers and/or percentages of events used as needed to describe the sample or data characteristics.
Outcome measures: These are primary and secondary study measures that are used to test the study hypotheses.
Process measures: These are 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: An event that represents significant divergence from the intended study design as described in the protocol.
Safety: An assessment of the condition of study subjects that examines potential risks, adverse events and reactions.
Safety measures: These are study measures that assess safety, such as blood pressure monitoring. These measures are used to assess safety of the study drug.
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: A list of each variable or item for each individual subject either in total or by condition in a table format.

2.0 Introduction

This is a data analysis plan for the study "3,4-methylenedioxymethamphetamine-assisted psychotherapy in Twelve Patients with Treatment-Resistant Posttraumatic Stress Disorder (PTSD."

3.0 Study Objectives

As stated in the protocol, the following main questions are to be explored in the proposed study:

1. Can MDMA, in the doses to be used in this study, be safely administered in the population of treatment-resistant PTSD patients without any serious adverse events?

2. Will patients receiving the larger, fully active dose of MDMA, in combination with non-drug assisted psychotherapy, demonstrate greater symptomatic improvement than patients given an active placebo dose of MDMA in combination with non-drug psychotherapy?

3. Will patients receiving three MDMA sessions in combination with non-drug psychotherapy demonstrate an additional improvement compared to patients receiving only two sessions?

4. Can treatment effects of MDMA-assisted psychotherapy be maintained beyond end of treatment?

3.1 Primary Objective

To evaluate changes in PTSD symptoms via CAPS scores gathered at baseline, three weeks after the second experimental session, and three weeks after the third experimental session.

3.2 Secondary Objectives

- To evaluate changes in PTSD symptoms as assessed via PDS at baseline, the day after each experimental session, and three weeks after the third experimental session.
- To evaluate PTSD symptoms measured by CAPS and PDS scores three weeks after the second Stage 2 experimental session, three weeks after the third Stage 2 experimental session and two months after the third Stage 2 experimental session.
- To formally or informally evaluate CAPS scores in participants who underwent an optional open label continuation for treatment non-responders (Stage 3).
- To evaluate changes in PTSD symptoms assessed via CAPS and PDS scores obtained two, six and twelve months after the third experimental session.

3.3 Safety Objectives

The safety objective presented in the protocol is item 1 in the Study Objectives listed above and has been formulated as individual objectives below:

- To assess blood pressure and pulse during experimental sessions using automated blood pressure and pulse monitoring equipment.
- To assess body temperature at regular intervals during experimental sessions.
- To assess experience of degree of psychological distress by repeated administration of the Subjective Units of Distress (SUD) during experimental sessions.

4.0 Study design

The study followed a randomized, active placebo-controlled, double-blind design, with subjects, psychotherapists and independent raters blinded to participant condition. Twelve subjects with treatment-resistant PTSD were randomly assigned after baseline assessment to receive either full dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h

later, or to an active placebo dose of 25 mg MDMA followed by 12.5mg MDMA 2.5h later. Participants underwent three sessions of MDMA-assisted psychotherapy scheduled to occur three to five weeks apart, 1 non-drug-psychotherapy session 24 h after each MDMA-session and 2-4 weekly integrative psychotherapy sessions after each MDMA session. PTSD symptoms were assessed by an independent rater once prior to MDMA-assisted psychotherapy, three weeks after the second MDMA-assisted session, three weeks after the third experimental session. After unblinding, active placebo participants had the opportunity to take part in an open-label continuation of the study, referred to here as "Stage 2." Data gathered three weeks after the third experimental session was treated as the baseline for Stage 2, and outcome measures were administered three weeks after the second and third experimental session. Originally outcome measures would also be given two, six and twelve months after the third experimental session, but the six-month evaluations were discontinued after January 2009 in line with the Amendment 5 of the protocol. Participants receiving the full dose in either Stage 1 or Stage 2 who did not show significant improvement in PTSD symptoms were offered the opportunity to take part in an open-label continuation of the study, "Stage 3", consisting of two additional MDMA sessions. During these sessions, they could receive 125 mg followed 2.5 hours later by 62.5 mg MDMA or a 20% larger dose of 150 mg MDMA, followed by a supplemental dose of 75 mg administered 2.5 hours later, unless contraindicated by safety parameters. Outcome measurements gathered at 2 months after the third experimental session will serve as baseline measures for Stage 3. Stage 3 was also cancelled in line with Amendment 5. Of the 12 participants who completed the study, only three participants underwent Stage 3.

4.1 Time and Events table

Please see attached document.

5.0 Measures

5.1 Outcome Measures

- Clinician-Administered PTSD Scale (CAPS) Global Score, subscale scores (B, C, D, F), Diagnostic criteria Met score, Associated Features (#26, 27, 28. 29. 30)
- PTSD Diagnostic Scale (PDS) Score, Rating, Impairment

5.2 Safety Measures

- Subjective Units of Distress (SUD)
- Vital signs (Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body temperature (BT))
- Spontaneously reported reactions during experimental sessions and seven days afterward
- Adverse events reported during the study
- General well-being assessment

5.3 Process Measures

Reactions to Research Participation Questionnaire – Short Form Revised (RRPQ)
Subject Belief of Condition Assignment

6.0 Analyses

6.1 Study population

See protocol. All participants were diagnosed with chronic PTSD, met DSM IV criteria, and had Global CAPS scores of 50 or greater upon enrollment. They had either undergone psychotherapy, pharmacotherapy or both without a significant reduction in PTSD symptoms.

All clinical data will be presented in tabular listings. All analyses will be carried out with SPSS of Version 12.0 or higher.

Definitions of subject populations for analysis:

All Enrolled: All participants who signed an informed consent form and completed baseline measures.
Intention to treat: All participants who were randomized to a condition and underwent at least one experimental session. All available data will be used.
Per Protocol: All participants who completed Stage 1 and underwent assessment of PTSD symptoms two months after the second experimental session. Analyses may be conducted with and without a participant who corresponds to a major protocol deviation.
Partial crossover: All participants who completed Stage 2 as well as Stage 1.
Extended Assessment 1: All participants who underwent assessment two, six and twelve months after their third Stage 1 or Stage 2 experimental session.
Extended Assessment 2: All participants who underwent Stage 3

6.2 Protocol Deviations

All protocol deviations will be included as a categorized listing. Subjects with minor deviations will be included in all analyses. Analyses will be performed with and without deviations to examine the effects of including them in an analysis. Secondary analyses may be conducted to examine interactions with certain characteristics within the subject population. If it is appropriate as indicated via analyses, subjects with major deviations will be excluded from the per protocol analysis and included in the intention to treat analysis. Safety analysis will include all enrolled subjects with all available data.

Possible deviation categories include:

- Entered study but did not meet entry criteria
- Developed withdrawal criteria during the study but were not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment
- Protocol procedure not performed per protocol
- Protocol procedure performed out of range
- Informed consent performed not per protocol

6.3 Participant Demographics and Background

Population: All enrolled and Per protocol

Categorical Data includes: Gender, age, ethnicity/race, trauma etiology, medical history, psychiatric history, physical examination, lab values, general well being

Descriptive Data includes: Number of years with PTSD, number and duration of past therapy for PTSD, number and duration of past medications for PTSD, number of incidences of prior ecstasy use

Format of presentation: Summary tables including frequency listings in total and by condition

Content of presentation: Gender, age, ethnicity/race, trauma etiology, number of years with PTSD, number and duration of past psychotherapies for PTSD, number and duration of past medications for PTSD, number of incidences of prior ecstasy use, percent co-morbidity, as computed by summing number of current psychiatric diagnoses other than PTSD.

6.4 Efficacy Analyses

Descriptive Data includes: CAPS (Global Score, selected subscale scores, and Diagnostic criteria met), PDS (Severity Score, Rating, Impairment)

Format of presentation: Summary tables including descriptive data presented in total and by condition. Descriptive data will also be provided for any additional analyses. When applicable, summary tables divided on the basis of a given demographic variable will be provided, when demographic variables may serve as the basis for additional or subsidiary analyses, as participant age, or gender

Content of presentation: CAPS (Global Score and subscales, Diagnostic criteria met, Associated Features), PDS (Severity Score, Rating, Impairment)

6.4.1 Main analyses

Goal: To determine if there is a main effect of condition on PTSD symptoms and criteria for meeting PTSD, three weeks after the second experimental session and three weeks after the third experimental session 1.

Population: Intention to Treat and Per protocol

Data included in analyses: CAPS (Global Score, subscales, and Diagnostic criteria met)

Format of analyses: Repeated-measures ANOVA. If multiple scores from a single scale are assessed, Bonferroni corrections were applied.

Time: Baseline, 3 weeks after Exp. Session 2, 3 weeks after Exp. Session 3

Between-groups factors: Condition (125 mg MDMA, 25 mg MDMA)

6.4.2 Additional analyses

Analysis #1

Goal: To determine if there is a main effect of condition on self-reported PTSD symptoms for meeting PTSD criteria, three weeks after the second experimental session and three weeks after the third experimental session 1.

Population: Intention to treat and Per protocol

Data included in Analyses: PDS Severity Score

Format of analyses: Repeated measures ANOVA

Between-groups Factor: Condition (125 mg MDMA, 25 mg MDMA)

Analysis #2

Goal: To determine if there is a main effect of condition and participation in partial crossover upon PTSD symptoms, meeting PTSD diagnostic criteria, and reduced psychological symptoms three weeks after the third experimental session, and three weeks after the third Stage 2 session.

Population: Intention to Treat, Per Protocol and Partial Crossover

Data included in analyses: CAPS (Global Score and subscales specified above, Diagnostic criteria met, Associated Features), PDS (Severity Score, Rating, Impairment)

Format of Analyses: Repeated measures ANOVA. If multiple scale scores from a single measure are analyzed, Bonferroni corrections will be applied.

Time: Baseline, 3 Weeks after Stage 1 Experimental Session 3, 3 weeks after Stage 2 experimental session 3

Between-groups factors: Condition (125 mg MDMA, 25 mg MDMA)

Analysis #3

Goal: To test for an effect of Stage on PTSD symptoms and meeting criteria for PTSD.

Population: Intention to Treat, Per Protocol and Partial crossover

Data included in analyses: CAPS (Global Score and subscales specified, Diagnostic criteria met, Associated Features), PDS (Severity Score, Rating, Impairment)

Format of Analyses: Repeated measures ANOVA or independent t-tests. If multiple scale scores from a single measure are analyzed, Bonferroni corrections will be applied.

Time: Baseline, 2 months after Stage 1 3rd Experimental Session, 2 months after 3rd Stage 2 Experimental Session

Between-groups factors: Condition (125 m MDMA, 25 mg MDMA)

Analysis #4

Goal: To determine whether there is a continued effect of MDMA-assisted psychotherapy 2, 6 or 12 months after the third experimental session through formal or informal analyses

Population: Extended Assessment 1

Data included in Analysis: CAPS (Global Score, Diagnostic criteria Score, Associated Features), PDS (Severity Score, Rating, Impairment)

Format of Analysis: Informal comparison of descriptive data for the three participants who underwent 2, 6 and 12 month assessment.

Time: Baseline, 2, months after Stage 1 or Stage 2 Experimental Session 3, 6 months after Stage 1 or Stage 2 Experimental Session 3, 12 months after Stage 1 or Stage 2 Experimental Session 3.

Demographic factors analysis

Goal: To test for a main effect of the basic demographic factors gender, age, number of years of psychotherapy and presence of additional affective disorders upon PTSD symptoms across both conditions, meeting PTSD diagnostic criteria, and reduced psychological symptoms and three weeks after 3rd Stage 1 experimental session

P*opulation*: Intention to treat, Per protocol

Data included in analysis: CAPS (Global Score and subscales, Diagnostic criteria met, Associated Features) and PDS (Severity Score, Rating, Impairment). Demographic variables will include gender, age, years of psychotherapy, presence of other affective disorder.

Format of analysis: Repeated-measures ANOVA for categorical data (gender, presence of additional affective disorder), linear regression for continuous data (age, years of psychotherapy)

Time: Baseline, End of Stage 1

Between group factors / independent predictors: Gender, age, years of psychotherapy, presence/absence of other affective disorder

6.4.3 Subsidiary analyses

Goal: To test for the source of variance of any potential interactions between demographic variables and outcome measures. These analyses will only be performed if any interactions are

found between specific criteria and efficacy data. NOTE: if there are no significant findings for given score, will not perform subsidiary analysis on specific score.

Population: Intention to Treat and Per Protocol

Data included in analyses: CAPS (Global Score and specified subscales, Diagnostic criteria met, Associated Features), PDS (Severity Score, Rating, Impairment)
If and only if there are systematic differences detected by chi square in a demographic variable (age, gender, # years psychotherapy).

Format of Analyses: A) Repeated measures analysis of variance using condition and demographic variable as between group variable and time of administration as repeated measure OR B) two separate repeated measures analyses of variance with condition as a between-group factor, one analyses with and one without members of specific category.

Time: Baseline, 3 weeks after 2rd Stage 1 experimental session, 3 Weeks After 3rd Stage 1 Experimental Session

Between-groups factors: Condition (125 mg MDMA, 25 mg MDMA); Demographic factor (e.g. male, female)

6.5 Safety Analysis

Population: All enrolled, intention to treat, per protocol, partial crossover, Extended Assessment 1 (when applicable), Extended Assessment 2 (when applicable)

Categorical data includes: Spontaneously reported reactions occurring seven days after an experimental session (maximum intensity, duration within 24 hrs of the experimental session, total duration across seven days), Adverse Events

Format of presentation: Summary tables of frequency listings in total, by condition (placebo, MDMA, partial crossover, Extended Assessment 1, Extended Assessment 2), by relatedness to study drug, by session number, by body system, by classification

Content of presentation: Specific spontaneously reported reactions by classification (across 7 days after an experimental session), number of spontaneously reported reactions, Adverse Events

Descriptive data includes: Physiological data (vitals, vital signs above cut-off and time point above cut-off during experimental sessions); psychological distress (SUD); Lab values

Format of presentation: Summary tables of frequency listings in total, by condition and by session number when applicable.

Content of presentation; Pre-drug average, maximum change (peak), and post-drug average values of physiological data (HR, SBP, DBP, BT); vital signs above cut-off and time point above cut-off during experimental sessions; psychological distress (SUD)

6.5.1 Main Analysis

Physiological Measures and SUD

Analysis #1
Goal: to test the presence of a main effect of condition (125 mg MDMA, 25 mg MDMA, 150 mg MDMA in Extended Assessment 2) on changes in vital signs and psychological distress,

Population: All enrolled, intention to treat, per protocol, partial crossover, Extended Assessment 2

Data included: Pre-drug average, maximum change (peak) and post-drug average SBP, DBP, HR, BT and SUD, number of participants with vital signs above clinical cut off and duration above clinical cut-off

Format of Analyses: One-way ANOVA per each experimental session, including sessions during Stage 1, Stage 2 and Stage 3

Between-Group Factor: Condition (125 mg MDMA, 25 mg MDMA, 150 mg MDMA in Extended Assessment 2)

Analysis #2

Goal: To test effects of condition, presence or absence of supplemental dose and time of session on physiological data and psychological distress during experimental sessions

Population: All enrolled, intention to treat, per protocol

Data included: Pre-drug average, maximum change (peak) and post-drug average SBP, DBP, HR, BT and SUD, number of participants with vital signs above clinical cut off.

Format of analysis: Repeated measures ANOVA

Time: Session (Experimental 1, Experimental 2, Experimental 3)

Between Groups Factors: Condition (125 mg MDMA, 25 mg MDMA) as between-group factor, and supplemental dose (given, not given) as second between-group factor.

Analysis #3

Goal: To test effects of condition, presence or absence of supplemental dose and time of session on physiological data and psychological distress during Stage 2 or Stage 3 sessions.

Population: Partial crossover, Extended Assessment 2

Data included: Pre-drug average, maximum change and post-drug average SBP, DBP, HR, BT and SUD, number of participants with vital signs above clinical cut off, and duration above clinical cut-off.

Format of analysis: Repeated measures ANOVA

Time: Crossover Session (Stage 2 Experimental Session 1, 2, and 3, Stage 3 Experimental sessions 1 and 2)

Between-Subjects factors: Supplement (present, absent)

6.5.2 Subsidiary analyses

Physiological and SUD:

Analysis #1

Goal: To test for the presence of interactions between demographic variables and condition on one or more physiological variable or psychological distress. Performed if and only if there are significant differences in representation of a given demographic variable or feature across conditions (as, more women in one condition than the other), or if doing so gathers essential information on study drug safety.

Population: All enrolled, intention to treat, per protocol, partial crossover

Data included in analyses: Peak SBP, DBP and HR, peak SUD

Format of Analysis: Two-way analysis of variance, one per experimental session in each stage

Between-group factors: Demographic variable (e.g. gender), Condition (125 mg MDMA, 25 mg MDMA).

Analysis #2

Goal: To determine if there is an effect for Stage (e.g. order of administration) upon measures of physiological response or psychological distress taken during full-dose MDMA sessions.

Population: Intention to treat, per protocol [125 MDMA only], partial crossover [previously assigned to 25 mg MDMA]

Data included in analyses: Pre-drug average, peak and post-drug average vital signs computed across all subjects averaged across 1) Randomized or 2) Open label full dose sessions

Format of analysis: Full repeated measures ANOVA

Between group factor: Blinding (Randomized, Open Label)

6.5.3 Adverse Events

Summary Tables

Goal: To present adverse events organized by drug dose, defined here as total amount of study drug per session near AE or reaction, including initial dose and supplement if administered, , seriousness, severity and relatedness to the study drug

Population: All enrolled, Intention to treat, Per protocol, Partial crossover, Extended Assessment 1, Extended Assessment 2

Categorical data includes: Number of AEs per subject; Number of severe AEs; Instances of occurrence of each spontaneously reported reactions by condition (MDMA, Placebo) and Stage (Stage 1, Stage 2); Adverse events (AE identity, seriousness (Yes/No), severity (mild, moderate, severe), onset, resolution, relatedness to study drug (not related, possibly related, probably related); Spontaneously reported reactions listed by MedDRA (Version 14) System Order Class

Format of presentation: This data will be presented in several summary tables of counts per subject, by drug dose, or across the course of the study, as appropriate for the data or descriptive statistics being listed.

Content of Presentation: Number of AEs per subject; Number of severe AEs; Instances of occurrence of each spontaneously reported reactions by condition (MDMA, Placebo) and Stage (Stage 1, Stage 2), number of severe spontaneously reported reactions;Adverse events (AE identity, seriousness (Yes/No), severity (mild, moderate, severe), onset, resolution, outcome, relatedness to study drug (not related, possibly related, probably related); Spontaneously reported reactions listed by MedDRA Version 14 System Order Class

Descriptive data includes: Overall number of AEs, severity of AEs, Peak Demeanor after each experimental and open label session, Overall number of spontaneously reported reactions, average reported severity of spontaneously reported reactions

Format of Presentation: Summary tables of frequency listings in total, by condition, by session, by subject and by condition

Content of Presentation: Adverse Event Listings (All possibly and probably related AEs, all AES occurring within seven days of drug administration, all severe AEs, and number of severe AEs by condition); AE or severity of AE and peak demeanor after each experimental or open label session by condition (MDMA, placebo, partial crossover).

Tabular Listing of Adverse Events

Goal: To follow guidance for display of adverse events

Population: All enrolled, intention to treat, per protocol, partial crossover, Extended Assessment 2

Data included: Per each AE; Subject number, Patient identifier
- Age, race, sex, weight (height, if relevant)
- Location of CRFs, if provided
- Adverse event description (preferred term, reported term)
- Duration of the adverse event
- Severity (e.g., mild, moderate, severe)
- Seriousness (serious/non-serious)
- Action taken (none, dose reduced, treatment stopped, specific treatment instituted etc.)
- Outcome (e.g., CIOMS format)
- Relatedness process of determination given if possible
- Date of onset or date of clinic visit at which the event was discovered
- Timing of onset of the adverse event in relation to last dose of investigational product (if or when applicable)
- Investigational product dose in absolute amount, mg/kg
- Duration of investigational product treatment (Stage 1, Stage 2, Stage 3)
- Concomitant treatment during study.

Format of presentation: All adverse events for each patient, including the same event on several occasions will be listed, giving both preferred term and the original term used by the investigator. The listing should be by treatment group and will include:

Analysis #1

Goal: To see if one or more demographic factor and condition alter the number and severity of adverse events and spontaneously reported reactions collected across the course of the study.

Population; All enrolled, intention to treat, per protocol, partial crossover, Extended assessment 1, Extended assessment 2

Data included: Number of AEs collected across Stage 1, Stage 2 and Stage 3, and any AEs collected before 2, 6 and 12 month follow up for Extended Assessment 1 participants, Number of severe AEs collected across Stage 1, Stage 2 and Stage 3 (when applicable), average severity rating of AEs occurring during the study, number of individual spontaneously reported reactions and average severity of self-reported reactions.

Format of analysis: Two-way ANOVA for gender, linear regression analysis for age

Between-groups factors: Condition (125 mg MDMA, 25 mg MDMA, 150 mg MDMA (when applicable)); gender; age

Analysis #2

*Goa*l: to see if there is an effect of presence versus absence of supplemental dose upon number of AEs and spontaneously reported reactions and number of severe AEs and spontaneously reported reactions.

Population: All enrolled, intention to treat, per protocol, partial crossover, extended assessment 2

Data included: Number of AEs across all study stages, number of severe AEs across all study stages

Format of analysis: One-way ANOVA

Between groups factor: Dosage (25 mg MDMA, 37.5 mg MDMA, 125 mg, 187.5 mg, 150 mg MDMA, 212.5 mg MDMA, 225 mg MDMA)
Analysis #3

Goal: To see if demographic variables interact with dose of study drug; performed if and only if a previous analysis establishes that gender, age or presence of another affective disorder produce an interaction with condition.

Population; All enrolled, intention to treat, per protocol, partial crossover, Extended assessment 1, Extended assessment 2

Data included: Number of AEs across all study stages, number of severe AEs across all study stages.

Format of analysis: Two-way ANOVA for categorical data, regression analysis for continuous data

Between-group factors: Demographic factor (gender (male, female), age, presence of another affective disorder), study drug dose (25 mg, 37.5 mg, 125 mg, 187.5 mg, 150 mg, 212.5 mg, 225 mg MDMA)

7.0 Process / Non-Outcome Measures

Descriptive listings will be presented in total and by condition for the data listed below.

Data includes: RRPQ Scores (Positive, Negative effects), Subject Belief of Condition Assignment (Condition, certainty)

Analyses

Goal: To determine the strength and degree of the study blind

P*opulation*: Per protocol and Intention to treat

Format of Analysis: chi-square or other categorical analysis

Between-group factors: Condition (125 mg MDMA, 25 mg MDMA); guesses of condition assignments by participant after each experimental session; guesses made at the end of Stage 1 by participants.

8.0 Interim Analyses

Preliminary data including outcome measures was presented at conferences during 2010 and 2011 but prior to publication.