

PROTOCOL MP-8

Summary of Changes

IND #63,384

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Amendment 1 Version 2: March 3, 2010

Amendment 2 Version 1: August 31, 2010

Amendment 3 Version 1: July 25, 2011

Amendment 4 Version 1: February 6, 2012

**A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of
MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans,
Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic
Stress Disorder (PTSD)**

SPONSOR

Multidisciplinary Association for Psychedelic
Studies (MAPS)
309 Cedar Street, #2323
Santa Cruz, CA 95060

SPONSOR DESIGNEE

Rick Doblin, Ph.D.
Phone number: 617-484-8711

CLINICAL INVESTIGATOR

Michael C. Mithoefer, M.D.
208 Scott Street
Mount Pleasant, SC 29464
Phone number: 843-849-6899

MEDICAL MONITOR

Julie Holland, M.D.
NYU School of Medicine
200 East 33rd Street, Suite 16H
New York, NY 10016
Voice mail: 212-358-5808

STUDY MONITOR

Berra Yazar-Klosinski, Ph.D.
Phone number: 831-429-6362
Fax number: 831-429-6370

1.0 MP8 Amendment 4 Rationale

The primary changes in Amendment 4 affect the study design cross over time point; timing of the primary end point; subject enrollment and review of the blood pressure readings. The primary changes are discussed below as well as in section 2.0 and 3.0. There are additional changes that do not effect design but provide additional detail to procedures, provide clarifications or are administrative changes. These are described in Section 3.0.

The protocol design has been amended to allow subjects in the low or medium dose group to cross over from Stage 1 to Stage 2 after 2 experimental sessions. Previously unblinding was after the 3rd experimental session. Unblinding will now happen after the PTSD symptom assessments post experimental session 2. The new primary end point for all subjects will be after the 2nd experimental session. Full dose subjects will continue in Stage 1 after unblinding so they will continue to have a total of 3 full dose experimental sessions. Stage 2 is unchanged, it continues to have 3 full dose experimental sessions. The crossover is three months earlier than the previous protocol version that required 3 experimental sessions for all subjects in Stage 1. This was done to decrease the amount of time low and medium dose subjects spend in Stage 1 and to increase our ability to evaluate whether our treatment method will involve two rather than three experimental sessions. Based on our experience with two subjects who have received low dose thus far, we believe it is safe to administer three low or medium dose sessions, but it may create an unnecessary hardship for participants by extending their treatment at low and medium doses. We believe that two sessions are likely to demonstrate significant separation between the low dose group, the medium dose group and the full dose group.

In addition, the number of participants has been increased from 16 to 24 and participants may now also include police officers and firefighters. Adding more subjects and opening enrollment to firefighters and police officers will increase the sample size and potentially open the study to more participants present in the local community, who may have similar service-related PTSD.

For subjects without a diagnosis of controlled hypertension, after viewing baseline values at the beginning of the session, the investigators will only view the blood pressure or pulse values in the case of a medical indication in order to improve the effectiveness of condition blinding. Concealment of the BP and pulse measurements from the therapists is expected to assist in maintaining the study blind by preventing the therapists from viewing physiological effects associated with MDMA and thus accurately guessing the condition allocation for a study participant. In the event of any medical indication, such as signs or symptoms that could be related to either hypertension, hypotension, tachycardia or bradycardia, the investigators have the option to begin observing the BP and pulse measurements during the session, to print out the results of measurements since the beginning of the session and to make more frequent measurements if judged necessary.

Changes were made to sections that are associated with the major changes discussed above these include updates to the protocol objectives, visit descriptions, time and events and analysis sections.

Grammatical changes were made throughout in order to accommodate the changes to the protocol. In addition, corrections to spelling and sentence structure have been updated for readability. These types of changes are not included in the detail below.

2.0 Systematic Changes Effecting Multiple Sections

Change #1: Throughout the protocol the number of subjects has been updated from 16 to 24. Wherever noted in the protocol, the subject breakdown has been changed to twelve subjects in the full dose group, six subjects in the active placebo group and six subjects in the low dose group. This was changed from, eight in the full dose, four in the active placebo group, and four in the medium dose group.

Sections Affected: 2.1 Introduction, paragraph 3; 4.3 MDMA Doses, Compounding, and Labeling, paragraph 2; 5.0 Protocol Design, paragraph 1; 5.2 Randomization and Subject Numbering, paragraph 1; 5.3 Recruitment and Subject Population, paragraph 1;

Justification: Enrolling more subjects allows an increase in sample size.

Change #2: Throughout the protocol the subject population has been amended to include firefighters and police officers in addition to veterans.

Sections Affected: 2.1 Introduction, paragraph 3 and 4; 5.0 Protocol Design, paragraph 1; 5.3 Recruitment and Subject Population, paragraph 1.

Justification: Expanding enrollment to firefighters and police officers.

3.0 Specific Protocol Changes

Change #3: Update the title of the protocol for subject number.

Sections Affected: Title page.

Rationale: Changed to match new protocol design.

Previously Read: A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 16 Veterans with Chronic Posttraumatic Stress Disorder (PTSD)

Now Reads: **A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)**

Change #4: Update study objectives to accommodate the change to sample characteristics from veterans only to include firefighters and police officers and the change in primary endpoint from two months after third experimental session in Stage 1 to one month after the second experimental session and the addition of the objective to assess the subjects' perception of the third experimental session.

Sections Affected: 3.0 Protocol Objectives, complete section.

Rationale: The primary endpoint was moved to after the second experimental session to accommodate the new study design. The assessment of the participants' perception of the third dose was added to help evaluate the benefit of three MDMA-assisted psychotherapy sessions.

Previously Read: The objective of this study is to explore the safety and estimate the effect size of efficacy for MDMA-assisted psychotherapy in veterans with PTSD, a group with a different index trauma from most subjects in prior investigations of this experimental treatment.

Primary Objective

- Estimate changes in PTSD symptoms via Clinician-Administered PTSD Scale (CAPS) in participants receiving low dose (active placebo), medium and full dose of MDMA in the randomized study arms, referred to as Stage 1.

Secondary Objectives

- Estimate changes in posttraumatic growth via Post Traumatic Growth Inventory (PTGI) scores in participants in each of three dose conditions in Stage 1.
- Estimate changes in quality of life via Global Assessment of Functioning (GAF) scores in participants in each of the three dose conditions in Stage 1.
- Estimate changes in symptoms of depression via Beck Depression Inventory-II (BDI-II) scores in participants in each of the three dose conditions in Stage 1.
- Assess self-reported sleep quality via the Pittsburgh Sleep Quality Index (PSQI) at baseline and the end of Stage 1.
- Estimate changes in Neuroticism-Extroversion-Openness Personality Inventory (NEO PI) scores in participants at the start and the end of Stage 1.
- Estimate PTSD symptoms via CAPS, posttraumatic growth via PTGI, depression symptoms via BDI-II, quality of life via GAF, sleep quality via PSQI and personality via NEO PI before and after enrollment in all participants enrolled in the open label study arm, referred to as Stage 2, at baseline and the end of Stage 2.
- Estimate PTSD symptoms via CAPS, posttraumatic growth via PTGI, personality changes via NEO PI, depression symptoms via BDI-II, quality of life via GAF and sleep quality via PSQI one year after the final experimental session for each participant.

- Assess the ability of the investigators and participants to accurately guess condition assignment when asked to do so after each experimental session.
- Explore the effects of each MDMA-assisted psychotherapy session upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).

Now Reads: The objective of this study is to explore the safety and estimate the effect size of efficacy for MDMA-assisted psychotherapy in veterans, firefighters and police officers with PTSD, a group with a different index trauma from most subjects in prior investigations of this experimental treatment.

Primary Objective

- Assess changes in PTSD symptoms via Clinician-Administered PTSD Scale (CAPS) global scores in participants receiving low dose (active placebo), medium and full dose of MDMA in the randomized study arms at baseline and the primary endpoint one month after the second experimental session.

Secondary Objectives

- Assess changes in posttraumatic growth via Post Traumatic Growth Inventory (PTGI) scores in participants in each of the three dose conditions at the primary endpoint.
- Assess changes in quality of life via Global Assessment of Functioning (GAF) scores in participants in each of the three dose conditions in Stage 1 at the primary endpoint.
- Assess changes in symptoms of depression via Beck Depression Inventory-II (BDI-II) scores in participants in each of the three dose conditions in Stage 1 at the primary endpoint.
- Assess changes in self-reported sleep quality via the Pittsburgh Sleep Quality Index (PSQI) in each of the three dose conditions at the primary endpoint.
- Assess changes in Neuroticism-Extroversion-Openness Personality Inventory (NEO PI) scores in each of the three dose conditions at the primary endpoint.
- Assess PTSD symptoms via CAPS, posttraumatic growth via PTGI, depression symptoms via BDI-II, quality of life via GAF and sleep quality via PSQI in participants in the full-dose condition two months after the third Stage 1 experimental session.
- Assess PTSD symptoms via CAPS, posttraumatic growth via PTGI, depression symptoms via BDI-II, quality of life via GAF, sleep quality via PSQI and personality via NEO PI at baseline and the end of Stage 2 in all participants enrolled in Stage 2.
- Assess PTSD symptoms via CAPS, posttraumatic growth via PTGI, personality changes via NEO PI, depression symptoms via BDI-II, quality of life via GAF and sleep quality via PSQI one year after the final experimental session for each participant.

- Assess the ability of the investigators and participants to accurately guess condition assignment when asked to do so after each blinded experimental session.
- Explore the effects of each MDMA-assisted psychotherapy session upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Assess the effects of a third full dose experimental session by comparing Global CAPS scores of full dose subjects at the end of Stage 1 to those at the end of Stage 2.
- Assess value of third experimental session in Stage 1 by collecting each full dose subject's perception of the third experimental session at the end of Stage 1 and Stage 2.
- Correlate adherence to the Treatment Manual with Global CAPS scores using adherence criteria ratings to assess videos of psychotherapy sessions.

Change #5: Remove comparison of Subjective Units of Distress (SUD) from safety objectives.

Sections Affected: 3.3 Safety Objective, second bullet point.

Rationale: This was removed to reflect the analysis plan.

Previously Read: Subjective Units of Distress (SUD) and vital signs (blood pressure, heart rate and temperature) will be measured during each experimental session, and comparisons will be made for SUD and vital signs between active placebo, medium-dose and full-dose conditions.

Now Reads: Subjective Units of Distress (SUD) and vital signs (blood pressure, heart rate and temperature) will be measured during each experimental session, and comparisons will be made for vital signs between active placebo, medium-dose and full-dose conditions.

Change #6: Update the timing of the primary endpoint and Stage 2 for active placebo and medium dose subjects to after the second experimental session.

Sections Affected: 5.0 Protocol Design, paragraph 2.

Rationale: The active placebo and medium dose groups cross over to Stage 2, two months earlier.

Previously Read: Prior to undergoing the first MDMA-assisted (experimental) session, all participants will undergo three 90-minute preparatory (introductory) non-drug psychotherapy sessions with a male and female co-therapist team. Participants will subsequently undergo three day-long MDMA-assisted psychotherapy sessions with

experimental sessions scheduled three to five weeks apart. All psychotherapy sessions will be recorded to audio and video.

Now Reads: Prior to undergoing the first MDMA-assisted (experimental) session, all participants will undergo three 90-minute preparatory (introductory) non-drug psychotherapy sessions with a male and female co-therapist team. Stage 1 of the study will consist of two blinded experimental sessions and, for the full dose group, one open-label experimental session, each lasting six to eight hours and scheduled three to five weeks apart. The study will be unblinded after the second experimental session in Stage 1 which constitutes the primary endpoint assessment. After unblinding, medium dose and active placebo subjects will have the opportunity to continue to open-label Stage 2 and full dose subjects will complete the third open-label experimental session. All subjects will complete a long-term follow-up visit 12 months after their final experimental session. All psychotherapy sessions will be recorded to audio and video.

Change #7: Update outcome assessments timing to one month after the second experimental.

Sections Affected: 5.0 Protocol Design, paragraphs 4 and 5.

Rationale: The primary endpoint was moved to accommodate the new study design.

Previously Read: The blinded independent rater, who will not be present during any psychotherapy sessions, will assess participant PTSD symptoms with CAPS, symptoms of depression with BDI-II, posttraumatic growth with PTGI, quality of life with GAF and sleep quality with PSQI at baseline, one month after the second experimental session, and the end of Stage 1. Changes in personality traits will be assessed via NEO PI at baseline and at the end of Stage 1.

When each subject completes the evaluation at the end of Stage 1, the blind will be broken for that subject. Participants who had been assigned to receive active placebo or medium-dose MDMA will subsequently have the opportunity to enroll in the open-label study arm, or “Stage 2.” Stage 2 must start within a maximum of 5 months after the participant finishes Stage 1. The open-label study arm will follow a similar sequence of events and procedures, except that there will be a single preparatory session, and all MDMA-assisted psychotherapy sessions will be open-label with an initial dose of 125 mg MDMA followed by an optional supplemental dose of 62.5 mg.

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

When each subject completes the evaluation at the primary endpoint, the blind will be broken for that subject. Participants who had been assigned to receive active placebo or medium-dose MDMA will subsequently have the opportunity to enroll in the open-label study arm, or “Stage 2.” Stage 2 must start within a maximum of 5 months after the participant finishes Stage 1. The open-label study arm will follow a similar sequence of events and procedures, except that there will be a single preparatory session, and all three MDMA-assisted psychotherapy sessions will be open-label with an initial dose of 125 mg MDMA followed by an optional supplemental dose of 62.5 mg.

Change #8: Update language for timing of interim analysis.

Sections Affected: 5.0 Protocol Design, paragraph 7.

Rationale: The interim analysis was updated to reflect the change in protocol design.

Previously Read: An interim analysis may be performed after all participants complete Stage 1 and the appropriate assessments, but before all participants have completed the 12-month follow-up. The interim data analysis will be conducted for safety and efficacy.

Now Reads: An interim analysis may be performed before all participants have completed the 12-month follow-up. The interim data analysis will be conducted for safety and efficacy.

Change #9: Provide more detail on the planned duration of the protocol for the different dose groups 6 months (full dose group) or four months (medium and active placebo groups) to complete after screening and baseline evaluation.

Sections Affected: 5.1 Planned Duration of Protocol, paragraph 1.

Rationale: The planned duration of the protocol was updated to reflect the two months removed from the time the active placebo and medium dose group are enrolled in Stage 2 of the study.

Previously Read: The randomized, double-blind, dose response controlled study segment (Stage 1) will take up to six months to complete after screening and baseline evaluation up until the evaluation at the end of Stage 1, two months after the last experimental session. The screening and baseline evaluation can take up to 2 months.

Now Reads: Stage 1 will take up to six months (full dose group) or four months (medium and active placebo groups) to complete after screening and baseline evaluation. The screening and baseline evaluation can take up to 4 months. In addition, if the length of time between the end of tapering and the first experimental session is longer than a month, the CAPS should be repeated to show consistency between this score and the baseline CAPS.

Change #10: Update to timing of unblinding to after the second experimental session in Stage 1.

Sections Affected: 5.2 Randomization and Subject Numbering, paragraph 1.

Rationale: Wording was updated to reflect the change in protocol design.

Previously Read: The participant, independent rater and both investigators conducting psychotherapy will be blind to condition assignment. Participants who drop out of the study or are withdrawn by the Clinical Investigator prior to the end of Stage 1 will be replaced until 16 participants have completed the study.

Now Reads: In all other cases, the blind will be maintained up through the primary endpoint assessment. The participant, independent rater and both investigators conducting psychotherapy will be blind to condition assignment, until that point, and the independent rater will remain blinded to condition assignment. Participants who drop out of the study or are withdrawn by the Clinical Investigator prior to the primary endpoint will be replaced until blinded data has been collected from 24 participants.

Change #11: Added definition for treatment resistance to include participants who discontinued treatment due to lack of tolerability

Sections Affected: 5.3 Recruitment and Subject Population, paragraph 1.

Rationale: Clarification of treatment resistance in inclusion criteria.

Previously Read: Not present.

Now Reads: Treatment resistance is defined as PTSD of at least six months duration where patients 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.

Change #12: Update Inclusion Criteria to include definition of treatment resistance.

Sections Affected: 5.3.1 Inclusion Criteria.

Rationale: The definition was added to provide clarity for enrollment requirements.

Previously Read: 3. have had at least one unsuccessful attempt at treatment with medication, such as an SSRI, SNRI, or mirtazapine, or one unsuccessful treatment with any form of psychotherapy for which there exists a controlled trial indicating efficacy in the treatment of PTSD. This includes cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, insight-oriented psychotherapy, and EMDR. Treatment with an SSRI or SNRI must have lasted for at least three months. Psychotherapy must have lasted for 6 months and included at least 12 sessions. Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.

Now Reads: 3. Have had at least one unsuccessful attempt at treatment for PTSD with medication, such as an SSRI, SNRI, or mirtazapine, or one unsuccessful treatment with any form of psychotherapy for which there exists a controlled trial indicating efficacy in the treatment of PTSD. This includes cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, insight-oriented psychotherapy, and EMDR.

OR who discontinued treatment due to either:

- Inability to tolerate psychotherapy for PTSD (e.g. persistent “over-engagement” when attempting Prolonged Exposure Therapy) or
- Inability to tolerate psychopharmacology for PTSD due to treatment-emergent side effects;

Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.

Change #13: Update wording to allow for subjects to appropriately seek new therapy if desired after the final experimental session and prior to long term follow up.

Sections Affected: 5.3.1 Inclusion Criteria.

Rationale: To clarify that it is acceptable to make changes to ongoing therapy after the final experimental session.

Previously Read: 5. If in ongoing psychotherapy at the time subjects are recruited into the study, participants may continue to see their outside therapist during the course of the study. Participants must sign a release for the investigators to communicate directly with their therapist. Subjects may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session 2 months after the third experimental session. Subjects who do not live within reasonable driving distance of the study site (equal to or less than an estimated two hours’ drive from the study site) must have a therapist in the area in which they live whom they can call on for support and evaluation if necessary;

Now Reads: 5. If in ongoing psychotherapy at the time subjects are recruited into the study, participants may continue to see their outside therapist during the course of the study. Participants must sign a release for the investigators to communicate directly with their therapist. Subjects may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session 2 months after the final experimental session. Subjects who do not live within reasonable driving distance of the study site (equal to or less than an estimated two hours’ drive from the study site) must have a therapist in the area in which they live whom they can call on for support and evaluation if necessary;

Change #14: Update the entry criteria restriction on past “Ecstasy” use to be over the last 10 years.

Sections Affected: 5.3.2 Exclusion Criteria.

Rationale: This criterion was updated to clarify the number of years of past use of ecstasy use.

Previously Read: 10. have used “Ecstasy” (material represented as containing MDMA) more than five times or at least once within 6 months of the MDMA session;

Now Reads: 10. Have used “Ecstasy” (material represented as containing MDMA) more than five times within the last 10 years or at least once within 6 months of the MDMA session;

Change #15: Clarification to the methods section to include wording on adherence to the Treatment Manual.

Sections Affected: 6.0 Methods, paragraph 1.

Rationale: Adherence to the Treatment Manual was added to the protocol ensure therapy is conducted the same across subjects.

Previously Read: This wording was not present.

Now Reads: The following outcome, safety and process measures will be used in the study. Investigators will follow the most recent version of the Treatment Manual in all matters relating to the psychotherapy sessions and follow-up. All psychotherapy sessions, including experimental sessions, will be recorded to audio and video, with all recordings preserved for research and training purposes.

Change #16: Add clarification to the SCID version and process, Structured Clinical Interview for Diagnoses I Research Version (SCID-I-RV) to assess eligibility based on Axis I diagnoses.

Sections Affected: 6.0 Methods, paragraph 5.

Rationale: Clarification of SCID.

Previously Read: Participants will also undergo the Structured Clinical Interview for Diagnoses (SCID) and assessment via CAPS for psychiatric diagnosis and to determine participant eligibility.

Now Reads: Participants will also undergo the Structured Clinical Interview for Diagnoses I Research Version (SCID-I-RV) to assess eligibility based on Axis I diagnoses, which includes a self-report questionnaire to focus on modules to use based on symptoms and assessment via CAPS for psychiatric diagnosis and to determine participant eligibility.

Change #17: Update wording to accommodate the time point in the amended study design. Personality will be assessed at baseline, at the primary endpoint, at the end of Stage 2, and at 12-month follow-up.

Sections Affected: 6.0 Methods, paragraph 7.

Rationale: Language was updated to reflect proper time points according to the amended protocol design.

Previously Read: Subjects will be instructed not to reveal to the independent rater their own opinion about which dose of MDMA they received. The rater will assess PTSD symptoms, quality of life, sleep quality, symptoms of depression and post-traumatic growth prior to MDMA-assisted psychotherapy at baseline, one month after the second experimental session and two months after the third experimental session. Personality will be assessed at baseline, at the end of Stage 1, at the end of Stage 2, and at 12 month follow-up.

Now Reads: Subjects will be instructed not to reveal to the independent rater their own opinion about which dose of MDMA they believe they received. The rater will assess PTSD symptoms, quality of life, sleep quality, symptoms of depression and post-traumatic growth prior to MDMA-assisted psychotherapy at baseline, one month after the second experimental session and, for full dose subjects, two months after the third experimental session. Personality will be assessed at baseline, at the primary endpoint, at the end of Stage 2, and at 12 month follow-up.

Change #18: Update wording to accommodate the amended study design change for full dose subjects.

Sections Affected: 6.1 Assessments and Measures, paragraph 1.

Rationale: Language was updated to clarify sequence of events in Stage 2.

Previously Read: The following outcome and safety measures will be employed in Stage 1 and Stage 2, following a similar sequence of events, except that participants in Stage 2 will have one and not three preparatory (introductory) sessions.

Now Reads: The following outcome and safety measures will be employed in Stage 1 and Stage 2, following a similar sequence of events to the full dose subject group in Stage 1, except that participants in Stage 2 will have one and not three preparatory (introductory) sessions.

Change #19: Add information regarding the use of the long-term follow up questionnaire.

Sections Affected: 6.1.1 Outcome Measures, paragraph 8.

Rationale: Clarification was added from MAPS updated protocol template.

Previously Read: Not present.

Now Reads: The long-term follow up questionnaire has been developed internally by the Sponsor to assess long-term benefits and harms of MDMA-assisted psychotherapy at the 12 month follow up visit. This questionnaire takes between five and ten minutes to complete.

Change #20: Update language to safety measures to include new procedures for monitoring and collecting data on blood pressure for subjects without a diagnosis of controlled hypertension he investigators will only view the blood pressure or pulse values in the case of a medical indication in order to improve the effectiveness of condition blinding

Sections Affected: 6.1.2 Safety Measures, paragraphs 1 and 3.

Rationale: Clarification was added to match new change in protocol to ensure that the clinical investigator remains blinded.

Previously Read: Participants will rate their current degree of subjective distress with a single-item, self-report scale, the SUD scale, repeatedly during the MDMA session, with the degree of distress marked along seven points. Subjective psychological distress will be measured periodically throughout each experimental session.

Blood pressure, heart rate (as pulse) and temperature will be assessed periodically during each experimental session. Blood pressure and pulse will be measured at the outset of the experimental session, once every 15 minutes for the first four hours of the MDMA-assisted session and every 30 minutes for another two hours. Participants with controlled hypertension will have blood pressure and pulse assessed every 15 minutes for the first five hours and every thirty minutes for the next three hours. More frequent measurements will be taken as per the judgment of the Clinical Investigator if the established thresholds of 160 systolic, 110 diastolic or pulse 110 are exceeded. Blood pressure and pulse will be assessed via an automatically inflating cuff. Body temperature will be assessed via tympanic thermometer every 60-90 minutes.

Now Reads: Safety measures will be applied as described below to minimize risks associated with drug-assisted psychotherapy sessions.

Participants will rate their current degree of subjective distress with a single-item, self-report scale, the SUD scale, repeatedly during the MDMA session, with the degree of distress marked along seven points. Subjective psychological distress will be measured periodically throughout each experimental session.

Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure, heart rate (as pulse) and temperature will be measured periodically during each experimental session. Blood pressure and pulse will be measured at the outset of the experimental session, once every 15 minutes for the first four hours of the MDMA-assisted session and every 30 minutes for another two hours. Participants with controlled hypertension will have blood pressure and pulse assessed every 15 minutes for

the first five hours and every thirty minutes for the next three hours. More frequent measurements will be taken as per the judgment of the Clinical Investigator. Blood pressure and pulse will be assessed via an automatically inflating cuff. Body temperature will be assessed via tympanic thermometer every 60-90 minutes. For subjects with a diagnosis of pre-existing controlled hypertension, the results of blood pressure and pulse measurements will be viewed by the investigators as the measurements occur. For subjects without a diagnosis of controlled hypertension, after viewing baseline values at the beginning of the session, the investigators will only view the blood pressure or pulse values in the case of a medical indication in order to improve the effectiveness of condition blinding. The night attendant will print out the blood pressure and pulse results after the session, make a back-up copy, and will seal both copies together in an envelope and write their initials over the seal. This envelope will be part of the source record and will be kept sealed until after unblinding occurs for that subject. In the event of any medical indication, such as signs or symptoms that could be related to either hypertension or hypotension, the investigators have the option to print out the results during the session.

Change #21: Add language describing safety measures that will be used.

Sections Affected: 6.1.3 Process Measures, entire section.

Rationale: Clarification was added to match new MAPS protocol template.

Previously Read: Not present.

Now Reads: 6.1.3 Process Measures

Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze video data from selected preparatory, experimental and integrative sessions. The elements included in adherence criteria are specific to each type of session. The goal of these ratings will be to correlate therapist adherence to the Treatment Manual with outcome as a part of the sponsor's ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.

Belief of condition assignment and certainty will be collected from each therapist responsible for treating the subject and the subject at the integrative session on the day after each blinded experimental session in Stage 1. At the primary endpoint, the Independent Rater for the study will also provide their guess and certainty of condition assignment prior to unblinding. These beliefs are collected as a part of the sponsor's ongoing initiative to optimize the double-blind as a part of dose response studies.

Subject perception of the third experimental session will be collected from each full dose subject at the primary endpoint in Stage 1 and then again at the end of Stage 1. Stage 2 participants will complete the perception of the third experimental session at the secondary endpoint and then again at the 2-Month Follow-up after the 3rd experimental session. These investigators will collect these perceptions in the source records as a part

of the sponsor's ongoing initiative to assess the therapeutic value of the third experimental session.

The Reactions to Research Participation Questionnaire (RRPQ) [91] is an assessment of causes for taking part in research and responses to the experience of being a research subject. Subjects will complete this measure during their 2-month follow-up, with exact time of completion varying in accordance with participation in the third open label experimental session in Stage 1 or in Stage 2. The RRPQ is intended to assess the subject's experience as a research subject, perceived reasons for consenting to be a research subject and perceived freedom to take part in the study.

Change #22: Updated Time and Events Tables to reflect new study design (See protocol MP-8 Amendment 4).

Sections Affected: Time and Events Tables Stage 1 and Stage 2.

Rationale: Time and Events were updated to show to flow of the amended protocol.

Previously Read: See protocol MP-8 Amendment 3.

Now Reads: See protocol MP-8 Amendment 4.

Change #23: Add information regarding adherence to the treatment manual.

Sections Affected: 6.2 Study Procedure, Visit Descriptions and Adherence, entire section.

Rationale: Adherence to the treatment manual was added to the protocol to ensure therapy is conducted in the same manner across subjects.

Previously Read: 6.2 Visit Descriptions

Now Reads: 6.2 Study Procedure, Visit Descriptions and Adherence

To ensure consistency of the manualized therapy, each type of visit described below must follow the Treatment Manual. Adherence to the manualized therapy will be reviewed by monitoring of data and or rating videos of these visits as part of the data review process. All criteria for a visit type should be completed as a part of the visit series, which may take place over more than one day.

Change #24: Add wording to include updated language regarding screening from MAPS protocol template.

Sections Affected: 6.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study, Visit 1), paragraph 1.

Rationale: Wording was added to align MAPS protocols.

Previously Read: Not present.

Now Reads: All individuals who are prescreened, as defined in this section, should be assigned a screening number and recorded on the Subject Screening Log where information on the selection of potential subjects in the trial should be collected. Prospective participants will be prescreened by telephone according to an IRB-approved script to learn if they meet basic eligibility criteria.

Change #25: Add wording to include updated language from MAPS protocol template referring to adhering to the manualized treatment.

Sections Affected: 6.2.2 Preparatory Sessions (Visits 2-4), paragraph 3.

Rationale: Wording was added to align MAPS protocols.

Previously Read: Not present.

Now Reads: Adherence criteria for preparatory sessions should be completed as a part of one of the three sessions. These elements do not have to be accomplished in any specific order or in every preparatory session. Generally, adherence criteria for these sessions include that the therapists will work with the subject to prepare for MDMA-assisted psychotherapy. The therapists and subject will seek to form a strong working relationship with each other, and they will help the subject prepare for upcoming experimental sessions. Preparatory sessions will promote a safe set and setting for confronting trauma-related memories, emotions, and thoughts, which is intended to develop therapeutic alliance.

Change #26: Extend the screening period to four months.

Sections Affected: 6.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study, Visit 1), paragraph 3, 6.2.2 Preparatory Sessions (Visits 2-4), paragraph 4.

Rationale: The screening period was extended to allow for proper screening of subjects.

Previously Read: All eligible participants must be enrolled prior to the second preparatory session (Visit 3) and in maximum two months after the screening starts.

Screening may take place over more than one day and up to one month prior to Visit 1 (enrollment).

Now Reads: All eligible participants must be enrolled prior to the second preparatory session (Visit 3) and in maximum four months after the screening starts.

Screening may take place over more than one day and up to four months prior to Visit 1 (enrollment).

Change #27: Update wording to accommodate the amended study design change of 2 experimental sessions for the low and medium dose groups.

Sections Affected: 6.2.3 MDMA Sessions [Visits 5, 9, and 14 (Visit 14 for full dose group only)], paragraph 1.

Rationale: Language was updated to note open label sessions according to the amended protocol.

Previously Read: 6.2.3 MDMA Sessions (Visits 5, 9, and 14)

All participants will receive three double-blind experimental sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. The first experimental session should happen within 6 weeks of enrollment.

Now Reads: 6.2.3 MDMA Sessions [Visits 5, 9, and 14 (Visit 14 for full dose group only)]

Subjects in Stage 1 will receive two experimental sessions of MDMA-assisted psychotherapy blinded with respect to dose, scheduled approximately 3-5 weeks apart. Subjects in the open label third experimental session in Stage 1 and open label Stage 2 will receive experimental sessions with the full dose of MDMA.

Change #28: Add wording to include updated language regarding adherence criteria from MAPS protocol template.

Sections Affected: 6.2.3 MDMA Sessions [Visits 5, 9, and 14 (Visit 14 for full dose group only)], paragraph 3.

Rationale: Adherence to the treatment manual was added to the protocol ensure therapy is conducted the same across subjects.

Previously Read: Not present.

Now Reads: Adherence criteria for experimental sessions should be completed as a part of each experimental session. These elements do not have to be accomplished in any specific order. Generally, adherence criteria for these sessions include that the therapists will create and communicate a setting of safety and support the subject during periods of inner focus. Therapists will use a largely nondirective approach, following the lead of the subject's inner healing intelligence. Therapists will provide encouragement for staying present with difficult experiences. Therapists may occasionally offer gentle guidance or redirection as a choice to encourage collaborative exploration if the subject repeatedly avoids trauma related material. Therapists will inquire about somatic symptoms and if necessary encourage release of tension through movement, in whatever way feels appropriate to the subject. Therapists will use music to support the experience without being intrusive.

Change #29: Add wording to include updated language regarding monitoring and blood pressure from MAPS protocol template.

Sections Affected: 6.2.3 MDMA Sessions [Visits 5, 9, and 14 (Visit 14 for full dose group only)], paragraph 7.

Rationale: Clarification was added to describe process that will ensure the investigator remains blinded.

Previously Read: Not present.

Now Reads: For subjects without a diagnosis of controlled hypertension, after viewing baseline values at the beginning of the session, the investigators will only view the blood pressure or pulse values in the case of a medical indication in order to improve the effectiveness of condition blinding. More frequent measures will be taken if the participant exhibits symptoms that could be related to hypertension, hypotension tachycardia or bradycarida. In the event of any medical indication, such as signs or symptoms that could be related to either hypertension or hypotension, the investigators have the option to print out the results during the session.

Change #30: Add wording to include updated language regarding adherence criteria from MAPS protocol template, as well as updating the heading.

Sections Affected: 6.2.4 Integrative Sessions 24 Hours after Experimental Session [Visits 6, 10, 15 (15 for full dose group only)], paragraph 2.

Rationale: Adherence to the Treatment Manual was added to the protocol ensure therapy is conducted the same across subjects.

Previously Read: 6.2.4 Integrative Sessions 24 Hours after Experimental Session (Visits 6, 10, 15)

Now Reads: 6.2.4 Integrative Sessions 24 Hours after Experimental Session [Visits 6, 10, 15 (15 for full dose group only)]

On the morning after the MDMA session, the participant will meet with both investigators during a 90-minute integrative psychotherapy session.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or all in each and every integrative session. Generally, adherence criteria for these sessions include discussing material that emerged during experimental sessions and helping participants integrate their experiences both internally and into daily life. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone or pager. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

Change #31: Add wording to include updated language regarding adherence criteria from MAPS protocol template.

Sections Affected: 6.2.5 Daily Telephone Contact for Seven days after an Experimental Session, paragraph 1.

Rationale: Adherence to the treatment manual was added to the protocol ensure therapy is conducted the same across subjects.

Previously Read: Not present.

Now Reads: Investigators will follow the most recent version of the Treatment Manual in all matters relating to follow-up subsequent to the experimental psychotherapy sessions.

Change #32: Update wording to accommodate the amended study design change.

Sections Affected: 6.2.6 Integrative Psychotherapy between Experimental Sessions, paragraph 1.

Rationale: Language was updated to reflect proper timing of integrative sessions according to the amended protocol.

Previously Read: The participant will have 60 to 90-minute scheduled non-drug psychotherapy sessions with both psychotherapist investigators during the interval between the first and second experimental session, between the second and third experimental sessions and after the third experimental session.

Now Reads: In addition to the session the morning after each experimental session, the subject will have two additional integrative psychotherapy sessions with the therapists lasting 90 minutes between experimental sessions and in the month following the last experimental session in each stage. The therapists may conduct more sessions if they and the subject deem it necessary.

Change #33: Add wording to include updated language regarding adherence criteria from MAPS protocol template.

Sections Affected: 6.2.6 Integrative Psychotherapy between Experimental Sessions, paragraph 2.

Rationale: Adherence to the Treatment Manual was added to the protocol ensure therapy is conducted the same across subjects.

Previously Read: Not present.

Now Reads: Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not

have to be accomplished in any specific order or all in each and every integrative session. Generally, adherence criteria for these sessions include integration of material that emerged as a part of experimental sessions and afterward into daily life. Therapists will validate the choices of the subject to communicate or not on these thoughts, feelings and experiences. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone or pager. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

Change #34: Update wording to accommodate the amended study design change. Added descriptive language regarding the change in the primary endpoint evaluation in Stage 1, occurring one month after the second blinded experimental session, unblinding and changed time of administration for the NEO-PI.

Sections Affected: 6.2.8 Evaluation Two Months after the Third Experimental Session (Visit 18) Full dose subjects only. (End of Stage 1), paragraphs 1, 2 and 3.

Rationale: Language was updated to reflect proper timing assessments according to the amended protocol.

Previously Read: 6.2.7 Evaluation One Month after the Second Experimental Session (Visit 13)

Participants will meet with the independent rater for a 90 to 120-minute evaluation one month after the second experimental session and prior to the third experimental session. The independent rater will administer the CAPS, BDI-II, PTGI (in reference to the start of the study), PSQI and GAF. Administration of CAPS may be recorded to video. Suicidality will be assessed with the C-SSRS. The measures are described earlier in “Assessments and Measures.”

Now Reads: 6.2.7 Evaluation at Primary Endpoint & Unblinding (Visit 13)

The primary endpoint evaluation in Stage 1 will occur one month after the second blinded experimental session. This visit will consist of two meetings that may be completed on separate days, one with the independent rater and the other with the therapists. The blinded independent rater will administer: CAPS to assess PTSD symptoms, BDI-II to assess depression symptoms, GAF to assess general psychological function, PTGI to assess post-traumatic growth (in reference to start of the study), PSQI to assess sleep quality and NEO PI to assess personality. The blinded independent rater will provide their belief of the subject’s condition assignment.

After completing all assessments and measures with the independent rater, the subject will meet with the therapists for approximately 30 minutes. Following the visit with the independent rater the blind will be broken for the subject’s condition assignment. The independent rater will remain blind to condition assignment at this time. The therapists will assess suicidality with the C-SSRS. General wellbeing will be assessed.

If the subject had been assigned to receive medium dose or low dose MDMA, the therapists will discuss enrollment in Stage 2. Low and medium dose subjects will not complete the third experimental session and associated integrative sessions in Stage 1. Participants who decline enrolling in Stage 2 will complete the Responses to Research Participation Questionnaire (RRPQ). If participants had been assigned to the full-dose condition in Stage I, they will provide their perceptions of the third experimental session at this point. The therapists will discuss scheduling the third open label full-dose experimental session and integrative sessions.

Change #35: Update wording to accommodate the amended study design change. The final evaluation for full dose subjects in Stage 1 will occur two months after the third experimental session.

Sections Affected: 6.2.8 Evaluation Two Months after the Third Experimental Session (Visit 18) Full dose subjects only. (End of Stage 1), paragraphs 1, 2 and 3.

Rationale: Language was updated to reflect proper timing of assessments according to the amended protocol.

Previously Read: 6.2.8 Evaluation Two Months after the Third Experimental Session (End of Stage 1)

The final evaluation in the double-blind portion of the study will occur two months after the third experimental session. Participants will meet the independent rater for 90 to 120 minutes. The independent rater will administer the CAPS, BDI-II, PTGI (in reference to the start of the study), PSQI, and NEO PI, and participants will complete C-SSRS, and the independent rater will assess participants on the GAF. Administration of CAPS may be recorded to video. Adverse Events and medications will be collected as described in Sections 8 and 9 of the protocol.

Now Reads: 6.2.8 Evaluation Two Months after the Third Experimental Session (Visit 18) Full dose subjects only. (End of Stage 1)

The final evaluation for full dose subjects in Stage 1 will occur two months after the third experimental session. Participants will meet the independent rater for 90 to 120 minutes. The independent rater will administer the CAPS, BDI-II, PTGI (in reference to the start of the study), and the PSQI. The independent rater will assess participants on the GAF. Administration of CAPS may be recorded to video.

After completing all assessments and measures at the evaluation at the end of Stage 1 with the independent rater, the full dose subjects will meet with the investigators for approximately one hour. The investigators will administer the C-SSRS, and the subjects will indicate their perceptions of a third experimental session. Subjects will complete the RRPQ.

Subjects will receive a memory aid card for use between this visit and the 12-month follow up. Subjects will use this card to record AEs, medications and changes in psychiatric status that they will be asked about at the termination visit. Memory aids will not be collected. Subjects may return to taking psychiatric medications from this point onward if necessary.

Change #36: Update wording to accommodate the amended study design change of the low and full dose subjects crossing to Stage 2

Sections Affected: 6.2.9 Opportunity for Participants in Active Placebo and Medium Dosage Condition to Enroll in Open-Label Study Segment ("Stage 2"), paragraph 1.

Rationale: Language was updated to reflect proper timing assessments according to the amended protocol.

Previously Read: After completing all assessments and measures at the evaluation at the end of Stage 1, the participant will meet with the investigators for approximately one hour, and the blind will be broken for that individual. Participants assigned to the full-dose condition and participants assigned to the other conditions who decline enrolling in Stage 2 will complete the Responses to Research Participation Questionnaire (RRPQ). The independent rater will remain blind to condition assignment at this time.

Now Reads: Active placebo and medium dose participants who elect to enroll in Stage 2 will undergo a course of therapy and evaluation nearly identical to the full dose group in Stage 1, but given in an open-label context.

Change #37: Addition of the subjects' value of the third experimental session. Subject perception of the third experimental session will be collected from each full dose subject at the primary endpoint in Stage 1 and then again at the end of Stage 1.

Sections Affected: 6.2.10 Open-Label Study Segment for Active Placebo and Medium Dosage Participants ("Stage 2"), paragraph 1 and 6.2.11 Assessment Two Months after Third Open-Label Session (End of Stage 2), paragraph 1.

Rationale: The assessment of the participants' perception of the third dose was added to help evaluate the importance of maintaining three experimental sessions

Previously Read: Not present.

Now Reads: Participants will give their perception of the third session one month after the second experimental session.

Change #39: Add wording to include updated language from updated MAPS protocol template for handling study procedures, early termination or long term follow up for participants that discontinue from the study early.

Sections Affected: 6.3 Removal of Participants from the Study, paragraphs 2, 3 and 4.

Rationale: Wording was added to align this protocol with other MAPS protocols.

Previously Read: Participants who withdraw will be clinically monitored after withdrawal, the cause of which will be recorded in the participant's source records and CRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE resolutions, if applicable.

Now Reads: If a subject develops any exclusion criteria that in the opinion of the Medical Monitor, affects the safety of the subject, including psychiatric diagnosis, pregnancy or excluded medications, the subject will discontinue treatment.

Subjects will be clinically monitored after discontinuation of treatment by at least one of the therapists. The cause of discontinuation will be recorded in the subject's source records and CRF. Whenever possible, the tests and evaluations listed for the primary endpoint and 12-Month Follow Up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the investigators, Medical Monitor and/or Sponsor.

Subjects who discontinue treatment prior to the primary endpoint will be replaced. Individuals who replace these subjects will be assigned the next available subject number. Subjects who discontinue treatment after the primary endpoint in Stage 1 will not be replaced. If Stage 1 subjects discontinue treatment before the primary endpoint, the site should contact the randomization monitor for replacement instructions. If there is an emergency requiring knowledge of subject's condition assignment, the blind may be broken for an individual subject. The investigator will be provided with sealed emergency unblinding envelopes corresponding to each Enrollment Code. These sealed envelopes will be stored in a secure limited access area and should remain sealed if there are no emergency unblinding events during the study. The therapists, independent rater, and subject will remain blind to condition assignment until unblinding at the primary endpoint. Unblinding at the primary endpoint will be done using the web-based randomization program. Detailed instructions will be provided to the site in a separate document.

Change #40: Add wording to include updated language regarding monitoring for treatment manual adherence from updated MAPS protocol template.

Sections Affected: 11.0 Study Monitoring, Auditing and Documentation, paragraph 1.

Rationale: Adherence to the treatment manual was added to the protocol to ensure that therapy is conducted in the same manner across study subjects.

Previously Read: The site will be monitored as appropriate for the rate of enrollment.

Now Reads: The site will be monitored as appropriate for the rate of enrollment in order to comply with GCP guidelines and to ensure validity of the study data. From the start of

the study, videos from selected sessions will be reviewed for adherence to the Treatment Manual and therapeutic alliance. Adherence will be checked by monitoring and by review of selected video data.

Change #41: Update the Data Analysis section to accommodate the amended primary end point, number of subjects and to clarify the planned analyses.

Sections Affected: 12.0 Data Analysis, paragraphs 1-9, 12 and 13.

Rationale: The data analysis section was revised to accommodate the change in the study design.

Previously Read: The sponsor will examine CAPS, BDI-II, PTGI, PSQI, GAF and NEO PI scores at baseline, one month after experimental session 2 (all measures except NEO PI), two months after experimental session 3 and at one-year follow-up in active placebo, medium-dose and full-dose conditions. The investigators will record peak blood pressure, heart rate and body temperature for participants during every session. Descriptive statistics will be calculated for all measurements overall and within the three dose conditions. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. Effect size of the three doses for all outcome measures for Stage 1, Stage 2, and one year post will be estimated using Cohen's techniques.

There may be preliminary examination of the data for safety and efficacy after all participants complete Stage 1, but before all participants have completed the 12-month follow-up. If conducted, the interim data analysis will be for safety and efficacy.

The sample selection is expected to produce acceptably homogeneous groups due to their all being veterans who served in the U.S. Armed Forces diagnosed with PTSD with CAPS scores of at least 50 who have not responded to treatment. There is no expectation that conditions will differ significantly in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, as depression.

Multivariate analysis of variance will be used to compare the active placebo, medium-dose and full-dose conditions for change in CAPS, BDI-II, PTGI, PSQI, GAF and NEO PI scores. If a significant result is found, post hoc analysis of variance will be conducted for CAPS, BDI-II, PTGI, PSQI, NEO PI and GAF scores separately. If PSQI scores cannot be examined sufficiently in this model, then analyses will compare available data through the use of difference scores. Further, if significant results are found for CAPS, BDI-II, or GAF scores, post hoc t-tests will be conducted to determine explicitly where the differences occurred.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The Sponsor will compare peak blood pressure, heart

rate and body temperature for participants after sessions using active placebo, medium-dose and full-dose MDMA.

Descriptive statistics will be computed for SOCQ scores completed after each MDMA-assisted psychotherapy session, and SOCQ scores will be compared across each of the three MDMA dose conditions and after full dose given during Stage 2. The data will be explored for effects of condition on responses to the SOCQ.

Now Reads: The Sponsor will judge the clinical and statistical significance of the study and estimate effect size and statistical power based on a comparison of observer-blind data collected at baseline and the primary endpoint using the primary outcome measure, which is the CAPS.

The sponsor will examine CAPS, BDI-II, PTGI, PSQI, and GAF scores at baseline and the primary endpoint, in active placebo, medium-dose and full-dose conditions. All analyses of data from the primary endpoint will contain blinded data from subjects who completed the post experimental session 2 outcome assessment.

Because of the change in study structure in this current amendment, the sponsor will examine blinded and open-label data collected two months after the third Stage 1 experimental session in two separate analyses, with one comparing scores from all three conditions occurring prior to this amendment and the other comparing baseline and primary endpoint scores to these scores in full dose participants only.

Descriptive statistics will be calculated for all measurements overall and within all three dose conditions. Descriptive statistics will be calculated for all measurements overall and within the three dose conditions. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. Effect size of the three doses for all outcome measures for primary endpoint, Stage 2 one month after experimental session 2, Stage 2 three months after experimental session 3, and one year post will be estimated using Cohen's techniques.

Average baseline and post-drug peak blood pressure, heart rate and body temperature will be logged automatically for participants during experimental sessions. The night attendant will print out the blood pressure and pulse results after the session, make a back-up copy, and will seal both the tape and the copy together in an envelope and write their initials over the seal. This envelope will be part of the source record and will be kept sealed until after unblinding occurs for that subject. The investigators will also record spontaneously reported reactions and AEs as described in section 8.3. Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The sponsor will informally or formally compare peak blood pressure, heart rate and body temperature for participants after sessions after low, medium or full dose MDMA. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

Subjects who discontinue treatment prior to the primary endpoint will be asked to complete an outcome assessment prior to continuing to the long-term follow-up. The data from these subjects will be tested for equivalence to data from subjects completing the study per protocol. If found to be equivalent, data from these subjects will be presented as an exploratory analysis to examine results without bias towards subjects more likely to complete the study per protocol.

There may be an interim analysis of the data that will not affect study conduct for safety and efficacy before all participants have completed the 12-month follow-up.

The sample selection is expected to produce acceptably homogeneous groups due to their diagnosis of with PTSD with CAPS scores of at least 50 who have not responded to treatment. There is no expectation that conditions will differ significantly in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, as depression.

Multivariate analysis of variance will be used to compare the active placebo, medium-dose and full-dose conditions for change in CAPS, BDI-II, PTGI, PSQI, GAF and NEO PI scores across both stages. If a significant result is found, post hoc analysis of variance will be conducted for CAPS, BDI-II, PTGI, PSQI, NEO PI and GAF scores separately. If PSQI scores cannot be examined sufficiently in this model, then analyses will compare available data through the use of difference scores. Further, if significant results are found for CAPS, BDI-II, or GAF scores, post hoc t-tests will be conducted to determine explicitly where the differences occurred.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The Sponsor will compare peak blood pressure, heart rate and body temperature for participants after sessions using active placebo, medium-dose and full-dose MDMA.

Descriptive statistics will be computed for SOCQ scores completed after each MDMA-assisted psychotherapy session, and SOCQ scores will be compared across each of the three MDMA dose conditions and after full dose given during Stage 2. The data will be explored for effects of condition on responses to the SOCQ.

Descriptive statistics will be calculated for subject's perceptions of a third experimental session. Mean, standard deviation and range of response will be examined. Perception of a third experimental session will be examined during Stage 1 and Stage 2, before and after participant have undergone a third experimental session. Perception of the third experimental session will be compared before and after completing a third experimental session and in low dose and full dose conditions.

The sponsor will collect measures of adherence to the manualized treatment across all sessions sampled. Descriptive statistics will be computed for each adherence scale within a given session. The sponsor will examine the factor structure of the measures of adherence to the treatment manual, and possible reformulation of the scale, as through

data reduction techniques, will be considered to streamline the measures and to combine the individual adherence scales into an overall measure of adherence or a smaller number of adherence scales, and correlate the adherence scale or scales with Global CAPS score at primary endpoint to investigate the effects of adherence to the treatment on reduction in PTSD symptoms.

Change #42: Updated the language to describe the effects that the amendment will have on the statistical power of the study design.

Sections Affected: 12.1 Statistical power, paragraph 1.

Rationale: The language was updated to reflect the increase in sample size and the effects this will have on statistical power.

Previously Read: Not present.

Now Reads: With the current amendment, the sponsor is increasing the group size in each condition, and all subjects will complete the primary endpoint. This may increase statistical power in this study, and will provide important estimates of effect size that can be used to develop a dose response model