PROTOCOL MP-8

Summary of Changes

IND #63,384

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Amendment 2 Version 1: August 31, 2010

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)

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Rationale

Amendment 2 makes several changes to the study design and a number of changes to protocol text prior to the start of the study. The protocol has been amended to include the addition of two new outcome measures, the Neuroticism Extroversion Openness Personality Inventory and the States of Consciousness Questionnaire, and updates terminology and measures to the most current version. This amendment revises language describing randomization, adverse event and concomitant medication collection, and visit scheduling to improve clarity. This amendment also adds two new inclusion criteria, in addition to improving wording for an inclusion criterion and audio and video recordings. The amended protocol no longer specifies that attendants match participant gender. Participants will receive memory aid cards to assist in their recall of any adverse events or medications when assessed at 12 month follow-up.

Changes to protocol

Change #1: This amendment limits the eligible subject population to include only veterans with chronic, treatment resistant PTSD. The rationale for this change is to study a homogenous subject group that can be more directly compared to the Sponsor's recently completed clinical trial, MP-1, under the same U.S. IND. Studying treatment resistant subjects with PTSD also lends significance to any improvements that occur with experimental treatment.

Previously read:
(Introduction) Since many veterans with PTSD have not been offered and/or have declined medication or psychotherapy for their PTSD, this study will include veterans with chronic PTSD of at least six months duration, but not necessarily treatment-resistant PTSD.

(Protocol Design) This randomized, double-blind study will examine the safety and efficacy of MDMA-assisted psychotherapy with 30, 75 or 125 mg MDMA in sixteen veterans diagnosed with PTSD arising from their service in the U.S. armed forces.

(Recruitment) Candidates for participation will be 16 veterans with PTSD arising from their service in the U.S. armed forces.

Now reads:
(Introduction) This study will include veterans with chronic PTSD of at least six months duration who satisfy PTSD diagnostic criteria despite having received prior treatment with either medication or psychotherapy.

(Protocol Design) This randomized, double-blind study will examine the safety and efficacy of MDMA-assisted psychotherapy with 30, 75 or 125 mg MDMA in sixteen veterans diagnosed with chronic, treatment-resistant PTSD arising from their service in the U.S. armed forces.

(Recruitment) Candidates for participation will be 16 veterans with chronic, treatment-resistant PTSD arising from their service in the U.S. armed forces.

(Inclusion criteria #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, and 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.

Sections Affected: Section 2.1 "Introduction"; Section 5.0 "Protocol Design"; Section 5.3 "Recruitment and Subject Population"; Section 5.3.1 "Inclusion Criteria"

Change #2: Throughout the protocol, the investigator previously referred to as the "principal investigator" will now be referred to as the "clinical investigator."

Sections Affected: New terminology throughout the protocol.

Change #3: Throughout the protocol, the time point previously referred to as "two months after the third experimental session" is now referred to as the "end of Stage 1." Likewise, the time point previously described as two months after the third open label session will now be referred to as "the end of Stage 2." The change in visit description was made in order to improve protocol clarity.

Sections Affected: New terminology throughout the protocol.

Change #4: Throughout the protocol, the measure of posttraumatic growth previously referred to as the PTGI-C is now referred to as the PTGI. Participants can complete the measure in reference to various events, e.g. drug administration or a traumatic event. The "original" and "current" formats are otherwise identical.

Previously read:
The Post Traumatic Growth Inventory-Current (PTGI-C) is an adaptation of the Post Traumatic Growth Inventory assessing perceived benefits or growth in the two weeks preceding administration, using the same items from the original measure but adapting language to reflect recent experiences. It is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; (relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life. Participants will complete the PTGI at the same point in time when they complete the CAPS and BDI.

Now reads:

The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life. In this study, participants will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions. Participants will complete the PTGI according to the Time and Events table.

Sections Affected: Section 6.1.1 "Outcome Measures" and new terminology throughout the protocol.

Change #5: The introduction has been updated to reflect the current state of the MAPS clinical development program. The study of MDMA-assisted psychotherapy in Israel is no longer active and an abbreviated Clinical Study Report is currently under development.

Previously read:
MAPS is currently sponsoring other Phase 2 studies in Switzerland and Israel.

Now reads:
MAPS is currently sponsoring another Phase 2 study in Switzerland.

Section Affected: Section 2.1 "Introduction"

Change #6: A new secondary outcome measure, the Neuroticism-Extroversion-Openness Personality Inventory (NEO-PI) has been added to the protocol. It is a measure of personality and will be administered at baseline, at the end of Stage 1 and Stage 2, and at the 12-month follow up. This measure will permit testing of the hypotheses concerning changes in five personality traits.

Previously Read: Not present.

Now Reads:
The NEO PI will serve as a measurement of personality [78]. The NEO PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model. Participants will complete the NEO PI according to the Time and Events table.

Sections Affected: Section 1.0 "List of Abbreviations"; Section 3.2 "Secondary Objectives"; Section 5.0 "Protocol Design"; Section 6.0 "Methods"; Section 6.1.1, "Outcome measures"; Time and Events tables; Section 6.2.1 "Prescreening, Screening and Baseline Evaluation"; Section 6.2.8 "Evaluation Two Months After Third Experimental Session (at the End of Stage 1)"; Section 6.2.11 "Evaluation 12 Months After Final Experimental Or Open Label Session"; Section 12.0 "Data analysis"

Change #7: A new secondary outcome measure, the States of Consciousness Questionnaire (SOCQ) has been added to the protocol. The measure will assess alterations in consciousness with a focus on changes related to mystical experiences after each MDMA-assisted psychotherapy session.

Previously Read: Not present.

Now reads:
The States of Consciousness Questionnaire (SOCQ) is a 100-item questionnaire based on the "Peak Experience Profile" designed by Pahnke and colleagues [79, 80]. Participants respond to the SOCQ using a six-point Likert-type scale anchored at 0=none at all and 5=extreme (more than ever before in my life). It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. The measure is a self-report instrument and takes approximately 20 to 30 minutes to complete. Participants will complete the SOCQ after each experimental session in accordance with the Time and Events table, completing the measure at any time between the end of an experimental session and prior to leaving the treatment facility the next day.

Sections Affected: Section 1.0 "List of Abbreviations"; 3.2 "Secondary Objectives"; Section 5.0 "Protocol Design"; Section 6.0 "Methods"; Section 6.1.1 "Outcome measures"; Time and Events tables; Section 6.2.3, "MDMA Session (Visits 5, 9, and 14)"; Section 12.0 "Data Analysis"

Change #8: Protocol objectives for the secondary measure the GAF were duplicated both in the section for secondary measures and safety measures. The objective was removed from the safety objectives.

Sections Affected: Sections 3.2 "Secondary Objectives" and 3.3 "Safety Objectives"

Change #9: Language describing the randomization and compounding procedures for the study has been updated to encompass a web-based randomization procedure under development.

Previously Read:
Within 24 hours of the first experimental session, each participant will be assigned to one of the three dose conditions; 30 mg (active placebo), 75 mg (medium dose) or 125 mg (full dose). Eight participants will be assigned to the full-dose condition, four participants to the 75 mg condition and four participants to the 30 mg active placebo dose condition. The study will employ a blinded randomization procedure that will maintain the 50/25/25% ratio while maintaining the blind and ensuring that each subsequent condition assignment is not predicated on the previous assignment. A randomization monitor will generate and maintain a list of random numbers between one and 100. A randomization list program or procedure will be run to assign participants to full, medium or active placebo dose MDMA to twenty containers randomly assigned a

number between 1 and 100. Prescription bottles will be randomly assigned a number between 1 and 100. The randomization monitor will also create replacement doses that retain the same ratio of experimental dose to active placebo dose condition. The randomization monitor will supervise the procedure of filling bottles with MDMA and lactose.

The investigators will contact the randomization monitor after enrolling a participant. The randomization monitor will provide the investigators with the bottle number to be used for the participant and with sealed envelopes that will permit unblinding for an individual subject if required. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, the blind may be broken for an individual participant by opening the appropriate envelope, which will be kept sealed in a locked safe in the investigator's office at the study site so it would be easily available in case of emergency. In all other cases, the blind will be maintained up through the assessment occurring eight weeks after the third experimental session. 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 Principal Investigator prior to the two-month follow-up will be replaced until 16 participants have completed the study.

(Under MDMA Doses, Compounding and Labeling) Initial and supplemental doses of lactose, in doses of equivalent dry weight, will be placed into gelatin capsules of identical appearance to those used for initial and supplemental dose MDMA by the pharmacist according to an equivalent procedure.

Now Reads:
For Stage 1, a randomization list will be prepared at the beginning of the study. A second list will be created to replace subjects who withdraw from the study and are unblinded. At least 24 hours before the first experimental session, each participant will be assigned to one of the three dose conditions; 30 mg (active placebo), 75 mg (medium- dose) or 125 mg (full dose). Eight participants will be assigned to the full-dose condition, four participants to the 75 mg condition and four participants to the 30 mg active placebo dose condition. The study will employ a blinded randomization procedure that will maintain the 50/25/25% ratio while maintaining the blind and ensuring that each subsequent condition assignment is not predicated on the previous assignment. Drug containers will be assigned a unique random number. Container assignments to each subject will be performed on a per experimental session basis, and the container will contain the initial and supplemental capsules for a single experimental session. This will be done by contacting the Randomization Monitor. The unblinded Randomization Monitor will also oversee drug encapsulation and labeling of drug bottles. Replacement doses for subjects who replace dropouts that retain the same ratio of condition assignment will also be created. The Randomization Monitor will provide the investigators with sealed envelopes that will permit emergency unblinding for an individual subject if required. In all other cases, the blind will be maintained up through the assessment occurring at the end of Stage 1. 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. Subjects who withdraw during Stage 2 and the follow-up portion of the study will not be replaced.

Section Affected: Section 5.2 "Randomization and Subject Numbering"; Section 4.3 "MDMA Doses, Compounding, and Labeling"

Change #10: The inclusion criterion requiring that women of childbearing potential have a negative pregnancy test and use effective birth control was reworded to make it clearer and more readable.

Previously Read:
13. are of childbearing potential who have a negative pregnancy test and agree to use an effective form of birth control.

Now Reads:
14. must have a negative pregnancy test if able to bear children, and agree to use an effective form of birth control.

Section Affected: Section 5.3.1 "Inclusion Criteria"

Change #11: A new inclusion criterion has been added to ensure that subjects are not concurrently participating in another clinical trial for the purpose of clarity in data analysis.

Previously Read: Not present.

Now Reads:
18. Agree to not participate in any other interventional clinical trials during the duration of this study.

Section Affected: Section 5.3.1 "Inclusion Criteria"

Change #12: A statement that described visit scheduling after the investigators determined a participant met all inclusion criteria was clarified.

Previously Read:
If, after reviewing all information, the investigators conclude that a participant is eligible they will arrange and schedule at least one introductory session.

Now Reads:
If, after reviewing all information, the investigators conclude that a participant is eligible they will enroll the subject in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

Section Affected: Section 6.0 "Methods"

Change #13: The protocol no longer requires the attendants be of the same gender as the participant. This will make locating attendants and scheduling experimental sessions easier and allow flexibility in accommodating participant requests. The attendants will still have all other qualifications described in the protocol. Participants concerns and preferences will continue to be regarded.

Previously Read:
Participants will remain at the study site overnight accompanied by a same-sex attendant. He or she will be of the same sex as the participant, will have a healthcare background, and will undergo specific training for the role.

Now Reads:
Participants will remain at the study site overnight accompanied by an attendant. He or she will have a healthcare background and will undergo specific training for the role.

Sections Affected: Section 5.0 "Protocol design"; Section 6.2.2. "Preparatory Sessions"

Change #14: Under Section 6.1.2 "Safety Measures," text describing the C-SSRS (measure of suicidal ideation and behavior) refers readers to the Time and Events table instead of listing each time point, elaborating only in cases where the administration happens more than once.

Previously Read:
The C-SSRS will be administered 24 times during the randomized study; at baseline, after the second preparatory session, twice during each experimental session (once just prior to drug administration and once five to six hours after drug administration), after each integrative session, on the first and last days of daily telephone contact occurring after an experimental session, and on the visit which takes place approximately two months after the third experimental session. Participants undergoing medication washout will complete the C-SSRS once prior to and once after medication washout, using the times above if possible but with additional measures used if none of the scheduled times occur just prior to or after medication washout.

Now Reads:
The C-SSRS will be administered by the investigators in accordance with the Time and Events table. The measure will be administered at baseline, during the second preparatory session, twice during experimental sessions (once before and once after drug administration), on two days of telephone contact, during each integrative psychotherapy session and at the evaluation at the end of Stage 1, end of Stage 2 and the 12 month follow-up. Participants undergoing medication washout will complete the C-SSRS before and after medication washout.

Section Affected: Section 6.1.2. "Safety Measures"

Change #15: The amendment now describes provisions to record the CAPS administration to video for the purpose of permitting independent raters to score the same

individual, thus allowing calculation of inter-rater reliability. This recording will be done at the request of the investigators and sponsor clinical research team.

Previously Read: Not present.

Now reads:
To establish Independent Rater reliability, the investigators will have the option to video record the screening CAPS interview in as many instances as necessary.

Section Affected: Section 6.2.1 "Prescreening, Screening and Baseline Evaluation (Pre-study, Visit 1)"

Change #16: A paragraph at the end of Section 6.2.1 "Prescreening, Screening and Baseline Evaluation discussing rescue medication has been removed from this section as the content already appears in Section 9.0, "Collection of Concomitant Medication".

Previously Read:
Participants may receive a designated rescue medication that may be administered in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual.

Now Reads: Not present.

Section Affected: Section 6.2.1, "Prescreening, Screening and Baseline Evaluation (Pre-study, Visit 1)

Change# 17: Commonly listed side effects have been added to the description of adverse event collection in Section 6.1.2 Safety Measures.

Previously Read: Not present.

Now Reads:
All adverse events (AEs) and spontaneously reported side effects will be collected during each experimental session and for 7 days after each session. Commonly expected side effects that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe. Common, expected side effects are defined as those most frequently reported in the literature and include: Anxiety, difficulty concentrating, dizziness, drowsiness, dry mouth, fatigue, headache, heavy legs, impaired judgment, impaired gait/balance, increased irritability, increased personal worries or rumination, insomnia, jaw clenching, tight jaw, lack of appetite, low mood, nausea, need more sleep, nystagmus, parasthesias, perspiration, restlessness, sensitivity to cold, thirst and weakness. Serious adverse events (SAEs), adverse events leading to subject withdrawal from the study, and changes to psychiatric status will be collected throughout the protocol. Medications used to treat the specified AEs will be collected during the study, and all changes to psychiatric medications will be collected throughout the study."

Section Affected: Section 6.1.2 “Safety measures”

Change #18: Participants will be provided with a memory aid card for use in collecting information about adverse events and medication use at 12-month follow up. Participants will receive the memory aid card at the visit after completing Stage 1 or Stage 2, as appropriate. Memory aid cards are intended to remind subjects of events occurring over the 10 month period until their follow-up visit. The memory aid card will not be collected.

Previously Read: Not present.

Now Reads:
(End of Stage 1) Subjects not moving on to Stage 2 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. Full dose subjects may return to taking psychiatric medications from this point onward if necessary.

(End of Stage 2) Subjects will continue on to the 12-month follow up visit. 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.

(Adverse Events) A Memory aid card will be provided to the subject on the last visit prior to the 12 month follow up to record information on medications taken to treat SAEs, AEs leading to withdrawal and psychiatric AEs during the period between the end of Stage 1 or end of Stage 2 and the 12 month follow-up evaluation. The memory aid card will not be collected, but information from the card will be used to aid the subjects in providing information to the investigator. This information may be collected by phone.

Sections Affected: Section 6.2.9 “Unblinding and Opportunity for Participants in Active Placebo and Medium Dosage Condition to Enroll in Open-Label Study Segment ("Stage 2")”; Section 6.2.11 “Assessment Two Months After Third Open Label Session”; Section 8.4, “Adverse Event Collection”

Change #19: Collection of adverse events and concomitant medications will now follow slightly different procedures than originally described. This change will optimize use of investigator time and AE collection during the follow-up period. The investigators will collect all serious adverse events and any adverse events leading to a change in psychiatric status during the course of the study prior to 12-month follow-up, and they will collect adverse events requiring medical attention up through the participant’s last two-month follow-up, either at the end of Stage 1 or Stage 2. Adverse events related to planned treatments or physician visits for a condition noted at baseline in the medical

history will not be collected unless there is an exacerbation of the condition. Any event that leads to withdrawal from the study will be collected.

Previously Read:
Adverse events and side effects will be collected during and after each experimental session. All serious adverse events (SAEs) and adverse events of concern to the participant will be collected throughout the protocol.

Spontaneously reported side effects will be recorded during all three experimental sessions and for a period of seven days after each experimental session for a total of 27 times. Serious adverse events (SAEs), adverse events of concern to the subject and any adverse events requiring medical intervention will be collected throughout the protocol. The investigators will also assess general well-being during each introductory session, at each integrative session and during telephone calls for seven days following integrative sessions that occur a day after an experimental session."

Adverse events that will be collected for the duration of the protocol are:

- Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions from MDMA administration throughout the study
- Any event of concern to the participant throughout the protocol
- Any adverse event leading to withdrawal from the protocol
- Common expected side effects will be collected on the day of MDMA administration and for seven days after administration

Now Reads:
Serious adverse events, adverse events and spontaneously reported adverse events ("side effects") will be collected during the study according to Section 8.

All adverse events (AEs) and spontaneously reported side effects will be collected during each experimental session and for 7 days after each session. Commonly expected side effects that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe.

Spontaneously reported side effects will be collected during the experimental session and during the seven days of telephone contact following the integrative sessions that occurs on the day after each experimental session.

Adverse events (AEs) that will be collected for the duration of the protocol are:

- All SAEs will be collected through termination.
- All AEs and common expected side effects will be collected on the day of MDMA administration and for seven days after each experimental session.
- Events requiring medical attention will be collected from the first experimental session through the subject's final assessment at the end of Stage 1 or Stage 2 (as appropriate).

- Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any AE leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

Sections Affected: Section 3.3 "Safety Objectives," under 3.0 "Protocol Objectives"; Time and Events Table, Section 6.1.2, "Safety Measures"; throughout Section 6.2 "Visit Descriptions"; Section 8.2, "Common Expected Side Effects"; Section 8.4 "Adverse Event Collection"

Change #20: Wording has been altered regarding concomitant medication collection and to further clarify when subjects must refrain from taking psychiatric medication and when they can resume medications.

Previously Read:
All medications, over the counter (OTC) and prescription will be collected from screening through 7 days after the last MDMA session. From 7 days after the last MDMA session through study termination only prescription or OTC medications taken to treat AEs will be collected.

Participant concomitant medications will be recorded during screening. If necessary, the investigators will make plans for tapering off and discontinuing any contraindicated medication at this time, in consultation with the prescribing physician. The investigators will request information about any changes in medication just prior to each MDMA-assisted psychotherapy session. Medications taken during the course of the protocol, including medications taken to treat AEs will be recorded on a concomitant medications CRF. Participants must be willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the MDMA session to avoid the possibility of interactions (the interval will be at least 5 times the particular drug's half-life).

Now Reads:
All medications, over the counter (OTC) and prescription will be collected from screening through 7 days after the final experimental session. From 7 days after the final experimental session through study termination only medications taken to treat SAEs and psychiatric AEs will be collected.

Concomitant medications will be recorded during screening. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the experimental session to avoid the possibility of drug interactions (the interval will be at least 5 times the particular drug's half-life). If necessary, the investigators will make plans for tapering off and discontinuing any

contraindicated medication upon enrollment, in consultation with the prescribing physician.

The investigators will request information about any changes in medication. Medications taken during the course of the protocol, including medications taken to treat AEs, will be recorded on a concomitant medications CRF. Participants must be willing to refrain from taking any psychiatric medications until after the end of Stage 1 or Stage 2, with the exception of gabapentin when prescribed for pain control. The investigators may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual).

Section Affected: Section 9.0 "Collection of Concomitant Medications"

Change #21: The Sponsor and not the investigator will perform data analyses for this study according to written Standard Operating Procedures. The wording was updated to reflect current practice.

Section Affected: Section 12.0 "Data analysis"

Change#22: Rather than stating that a participant's full name or address will be removed from a session recording, the protocol states that full names or addresses will not appear on session recordings. Investigators will be diligent about withholding a participant's full name and address during a recording and the information will not be written down.

Previously Read:
Full names and addresses, if they appear in these recordings, will be edited out of the recording before the tape is seen by anyone other than the study participant, the investigators present at the session, and the designated audio/video technician who has signed a confidentiality agreement.

Now reads:
(Confidentiality) Full names and addresses will not appear in these recordings.

(Appendix B) Full names and addresses will not appear in video or audio recordings.

Section Affected: Section 13.1 "Confidentiality"; Appendix B "Audio and Video Recording"

Change #23: Wording for record retention practices was clarified to reflect current practice.

Previously Read:
Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. "Essential documents" are defined as

documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained Record Retention Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records.

Now Reads:
Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the Investigator Site File (ISF). It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Section Affected: Section 14.0 "Record Retention"

Change #24: Integrative psychotherapy sessions will no longer be scheduled at different times for subjects based on where they reside, to avoid stratifying subjects. After the integrative session the day after an experimental session, the remaining two visits will be scheduled to happen before the next experimental session.

Previously Read:
After undergoing three 90-minute non-drug introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions scheduled three to five weeks apart, during which they will randomly receive either the active placebo, medium-dose or full-dose MDMA on all three occasions. Participants will undergo one non-drug-psychotherapy session the day after each experimental session and at least two additional 90 minute non-drug integrative psychotherapy sessions between experimental sessions. For subjects who live within easy driving distance of the study site (equal to or less than an estimated two hours drive time of the site), these integrative psychotherapy sessions will be scheduled approximately a week apart. For subjects living farther away, these sessions may be scheduled at less regular intervals to accommodate travel logistics (for example, two may occur in the week following the preceding experimental session and the other might occur a day or two prior to the subsequent experimental session).

Now Reads:
After undergoing three 90-minute non-drug introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions scheduled approximately three to five weeks apart, during which they will randomly receive either the active placebo, medium-dose or full-dose MDMA on all three occasions. Participants will undergo one non-drug integrative psychotherapy session the day after each experimental session and at least two additional 90 minute non-drug integrative psychotherapy sessions between experimental sessions.

Section Affected: Section 6.0 "Methods"