PROTOCOL MP-8

IND #63,384

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Amendment 1: March 3, 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)

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

SPONSOR DESIGNEE
Rick Doblin, Ph.D.
[redacted]

PRINCIPAL INVESTIGATOR
Michael C. Mithoefer, M.D.
[redacted]

MEDICAL MONITOR
Julie Holland MD
[redacted]

STUDY MONITOR
Valerie Mojeiko
[redacted]

For trial related emergencies: Phone number [redacted]

Rationale

The amendment addresses concerns voiced by the Institutional Review Board (IRB) on reviewing the study protocol. Language was provided to clarify the intention of the preliminary examination of data. The amendment includes language clarifying the intention of the preliminary examination of the data and the addition of inclusionary and exclusionary factors addressing issues of monitoring participant safety, risk to self and risk to others. The amendment does not include any changes in study design or outcome assessment, and changes in procedure involve contingency plans to deal with specific risks and do not involve any change in drug administration, psychotherapy or measurement.

At the request of the IRB, the protocol contains an additional inclusionary criteria, that of providing a contact person who can be reached in case of emergency, and an additional exclusionary factor, that of being a risk to others. The protocol lists testing for hepatitis C virus as well as HIV testing in screening. The clarification that sponsor and investigators will follow participant pregnancies occurring during the study period after at least one experimental session through outcome.

The protocol also now contains definitions for several points of reference, including assessment of suicide risk and reasonable driving distance from the study site. Additional changes involve clarification concerning inclusion of sponsor coverage for any tests performed solely to determine study eligibility, presentation of a contingency plan for dealing with suicidal intent and administrative changes. The amendment also contains clarification to the Informed Consent process for stage 2.

Summary of Changes, listed in order of appearance in the amended protocol

Change 1: Section 5.0, "Protocol Design", p. 15, seventh paragraph in section.

Previously read: "There will be preliminary examination of the data before all participants have completed the 12-month follow-up."

Now reads: "There will be preliminary examination of the data after all participants complete experimental sessions and the two-month follow-up, but before all participants have completed the 12-month follow-up. The interim data analysis will be conducted for safety and efficacy."

Rationale: The protocol now offers specific information about the timing of the interim analysis and states that it is for safety and efficacy.

Change 2: Section 5.2, "Randomization and Subject Numbering," p. 16, second paragraph in section.

Previously read: "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. 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."

Now reads: "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 will be easily available in case of emergency."

Rationale: The protocol now provides information on how unblinding for an individual participant would be performed in case of medical emergency.

Change 3: Section 5.3.1, "Inclusion Criteria," p. 17, inclusion criteria #4.

Previously read: "4. If in ongoing psychotherapy at the time they are recruited into the study, participants may continue to see their outside therapist during the course of the study. They must sign a release for the investigators to communicate directly with their therapist. They 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 must have a therapist in the area in which they live."

Now reads: "4. If in ongoing psychotherapy at the time they are recruited into the study, participants may continue to see their outside therapist during the course of the study. They must sign a release for the investigators to communicate directly with their therapist. They 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."

Rationale: The definition of reasonable driving distance to the study site is provided.

Change 4: Section 5.3.1, "Inclusion Criteria," p. 18.

Previously read: Previously did not contain inclusion

Now reads: Contains inclusion #14, "must provide a contact (relative, spouse, close friend or other caregiver) who is willing and able to be reached by the investigators in the event of a participant becoming suicidal;"

Rationale: The protocol will now require participants to provide investigators with an emergency contact who may be reached in case of medical emergency, including suicidality.

Change 5: Section 5.3.2, "Exclusion Criteria," p. 19.

Previously read: "8. would present a serious suicide risk or who are likely to require hospitalization during the course of the study."

Now reads: "8. would present a serious suicide risk, as determined through psychiatric interview, responses to CSSRS and through the clinical judgment of the investigator, or who, in the judgment of the investigator, are likely to require hospitalization during the course of the study."

Rationale: Description of assessment of suicide risk is provided within the exclusionary criteria.

Change 6: Section 5.3.2, "Exclusion Criteria," p. 19.

Previously read: Previously did not contain this exclusion.

Now reads: "9. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist;"

Rationale: The protocol will now exclude participants determined to pose a risk to others.

Change 7: Section 6.0, "Methods," p. 19, second paragraph on section.

Previously read: "*Additional screening for specific conditions*: After this evaluation and completion of any recommended treatment, if the Hepatitis C is judged by this physician to be relatively stable and of mild severity the person may be enrolled if there are no other contraindications."

Now reads: "After this evaluation and after completion of any recommended treatment, if the Hepatitis C is judged by this physician to be relatively stable and of mild severity the person may be enrolled if there are no other contraindications."

Rationale: The protocol clarifies that participants must undergo appropriate course of treatment for hepatitis C before enrolling in the study.

Change 8: Section 6.0, "Methods," p. 20, under "Additional Screening", third paragraph in section.

Previously read: "If the potential subject has well-controlled hypertension and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam or ECG,

and if the Principal Investigator judges their overall health and other cardiovascular risk factors to be acceptable (family history, smoking, lipid levels, body weight, level of physical activity) they will be referred for exercise testing by a cardiologist and for carotid ultrasound. If these tests fail to reveal evidence of significant vascular disease or other cardiovascular disease the person may be enrolled if there are no other contraindications."

Now reads: "If the potential subject has well-controlled hypertension and no other evidence of cardiovascular or cerebrovascular disease by history, physical exam or ECG, and if the Principal Investigator judges their overall health and other cardiovascular risk factors to be acceptable (family history, smoking, lipid levels, body weight, level of physical activity) they will be referred for exercise testing by a cardiologist and for carotid ultrasound. If these tests fail to reveal evidence of significant vascular disease or other cardiac disease the person may be enrolled if there are no other contraindications. Participants taking one or more antihypertensives may be enrolled in the study. The investigators will record and review medications used to control hypertension prior to enrollment."

Rationale: The protocol clarifies the nature of enrolling participants with controlled hypertension so that it can include people taking one or more antihypertensive medication but that the investigators will record and review medications prior to enrollment.

Change 8: Section 6.0, "Methods," p. 20, fifth paragraph in section.

Previously read:"For subjects who live within easy driving distance of the study site, these integrative psychotherapy sessions will be scheduled approximately a week apart."

Now reads:"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."

Rationale: The definition of reasonable driving distance to the study site is provided.

Change 9: Just after Section 6.1, "Assessments and Measures" and prior to Section 6.2, "Visit Descriptions," Time and Events table, p. 24

Previously read: Clinical LabTests, w/ HIV

Now reads: Clinical LabTests, w/ HIV, HCV test

Rationale: The protocol now expressly addresses screening for hepatitis C virus (HCV)

Change 10: Section 6.2.1, "Prescreening, Screening and Baseline Evaluation," p. 26, first paragraph on section.
Previously red: "After giving written informed consent each participant will be assigned a screening number. The screening number will be used on all subject records prior to

enrollment. Participants will provide a medical and psychological history through interview and will undergo a general physical examination performed by a physician who is not one of the investigators. The examination will involve the following procedures: blood pressure, pulse, height, weight, body temperature, examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities, brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function) , electrocardiogram (ECG), clinical laboratory assessments to determine study eligibility (see 10.0 for list of laboratory tests). In addition, Human Immunodeficiency Virus (HIV) serology will be performed. If there is a confirmed positive HIV serology it will be kept confidential with the exception of reporting to the South Carolina Department of Health as required by law, with the Department of Health informing the home state of any individual not residing in South Carolina. Appropriate referral for counseling and treatment will be made if necessary. The clinical laboratory values will not be captured in the Case Report Form (CRF), but will be used to establish eligibility and will be kept with the subject's source record. A urine-dip pregnancy test for females of childbearing potential will be performed as well. If, upon examination, there are questions raised about possible medical problems, the investigators will request a review of participant medical records and request additional tests or assessments as indicated. If it is determined that the participant has Hepatitis C or well-controlled hypertension, further evaluation will be performed as described in section 6.0."

Now reads: "After giving written informed consent each participant will be assigned a screening number. The screening number will be used on all subject records prior to enrollment. Participants will provide a medical and psychological history through interview and will undergo a general physical examination performed by a physician who is not one of the investigators. The examination will involve the following procedures: blood pressure, pulse, height, weight, body temperature, examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities, brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function) , electrocardiogram (ECG), clinical laboratory assessments to determine study eligibility (see 10.0 for list of laboratory tests). In addition, Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) serology will be performed. If there is a confirmed positive HIV serology, it will be kept confidential with the exception of reporting to the South Carolina Department of Health and Environmental Control as required by law, with the Department of Health informing the home state of any individual not residing in South Carolina. Likewise HCV serology will be kept confidential except for reporting to the South Carolina Department of Health and Environmental Control within seven days of discovery as required by law. Appropriate referral for counseling and treatment will be made if necessary. The clinical laboratory values will not be captured in the Case Report Form (CRF), but will be used to establish eligibility and will be kept with the subject's source record. A urine-dip pregnancy test for females of childbearing potential will be performed as well. If, upon examination, there are questions raised about possible medical problems, the investigators will request a review of participant medical records and request additional tests or assessments as indicated. If it is determined that the participant has Hepatitis C or well-controlled hypertension, further evaluation will be performed as described in section 6.0."

Rationale: The protocol now expressly addresses screening for hepatitis C virus (HCV) and describes appropriate required reporting of any positive HCV screen.

Change 11: Section 6.2.1, "Prescreening, Screening and Baseline Evaluations," p. 26, third paragraph in section.

Previously read: "A blinded independent rater who will not be present during any of the therapy sessions will administer the CAPS and assess the participant on the GAF. The C-SSRS will also be administered at screening to assess suicide risk. The participant will complete the BDI and PTGI-C."

Now reads: "A blinded independent rater who will not be present during any of the therapy sessions will administer the CAPS and assess the participant on the GAF. The C-SSRS will also be administered at screening to assess suicide risk. Suicide risk will also be assessed via psychiatric interview. The principal investigator and independent rater will use medical records, communication with the participant's treating psychiatrist or therapist if applicable and psychiatric interview to assess potential risk to others. The participant will complete the BDI and PTGI-C."

Rationale: The protocol describes assessment of suicide risk in more detail.

Change 12: Section 6.2.3, "MDMA Session," p. 28, second paragraph in section.

Previously read: "On the day of the MDMA session, the participant will arrive approximately one to one and a half hours prior to the MDMA session. Continuing eligibility will be confirmed, with confirmation of eligibility including a urine drug screening and, if appropriate, a urine pregnancy test. If the subject continues to meet criteria and the participant reports that he/she followed appropriate rules and restrictions, the session will proceed; a positive pregnancy screen is cause for withdrawal from the protocol, a positive drug screen will be reviewed by the investigator and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study."

Now reads: "On the day of the MDMA session, the participant will arrive approximately one to one and a half hours prior to the MDMA session. Continuing eligibility will be confirmed, with confirmation of eligibility including a urine drug screening and, if appropriate, a urine pregnancy test. If the subject continues to meet criteria and the participant reports that he/she followed appropriate rules and restrictions, the session will proceed; a positive pregnancy screen is cause for withdrawal from the protocol, a positive drug screen will be reviewed by the investigator and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study. The sponsor and principal investigator will follow any pregnancy detected after the occurrence of at least one experimental session to outcome."

Rationale: The protocol now indicates that the sponsor and investigator will follow any pregnancy occurring after at least one experimental session to outcome.

Change 13: Section 6.2.5, "Daily Telephone Contact for Seven Days After an Experimental Session," p. 31, second paragraph in section.

Previously read: Not present.

Now reads: "If the investigators are unable to reach a subject by telephone despite repeated attempts, every effort will be made to contact their outside physician or a family member to be sure they receive any support they need. If the investigators eventually contact the person, this participant would be permitted to remain enrolled in the study only if measures could be put in place to assure that such a problem would not recur."

Rationale: The protocol describes a contingency plan for cases where the investigators are unable to contact a participant during the time of telephone contact.

Change 14: Section 6.2.8, "Unblinding and Opportunity for Participants in Active Placebo and Medium Dosage Condition to Enroll in Open-Label Study Segment ("Stage 2")," p. 32, second paragraph in section.

Previously read: "After unblinding, the investigators will provide Stage 2 consent materials to all participants who had been assigned to the active placebo and medium-dose conditions. Participants who elect to enroll in Stage 2 will undergo a course of therapy and evaluation nearly identical to the randomized study, but with full-dose MDMA given in an open-label context. They must give written, informed consent before enrolling in Stage 2."

Now reads: "After unblinding, the investigators will ask all participants assigned to active placebo or medium dose MDMA if they wish to enroll in Stage 2. Participants who elect to enroll in Stage 2 will undergo a course of therapy and evaluation nearly identical to the randomized study, but with full-dose MDMA given in an open-label context. The investigators will consider participants who have completed all Stage 1 study visits and who do not wish to enroll in Stage 2 as having completed the study. These individuals will complete the RRPQ."

Rationale: The protocol clarifies that a single consent form shall be used for this study, and that signing the consent form indicates a willingness to take part in Stage 2, and that declining to take part in Stage 2 upon unblinding will not be treated as study completion.

Change 15: Section 7.4.8, "Reproductive and Developmental Risks," p. 40, only paragraph

Previously read: "Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this

association, as discussed below in the "Pharmacology" section and in the Investigator's Brochure [150, 151]. Pregnant and lactating women will be excluded from participation in the proposed protocol, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to use birth control during the period of the protocol."

Now reads: "Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association, as discussed below in the "Pharmacology" section and in the Investigator's Brochure [150, 151]. Pregnant and lactating women will be excluded from participation in the proposed protocol, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to use birth control during the period of the protocol. If any participant becomes pregnant after the occurrence of at an experimental session, the sponsor and principal investigator will follow the pregnancy to outcome."

Rationale: The protocol now indicates that the sponsor and investigator will follow any pregnancy occurring after at least one experimental session to outcome.

Change 16: Section 12.0, "Data Analysis," p. 47, second paragraph in section

Previously Read: Not present

Now Reads: "There will be preliminary examination of the data after all participants complete experimental sessions and the two-month follow-up, but before all participants have completed the 12-month follow-up. The interim data analysis will be conducted for safety and efficacy."

Rationale: The protocol now offers specific information about the timing of the interim analysis and states that it is for safety and efficacy.

Change 17: Section 13.0, "Informed Consent," p. 48, second paragraph in section.

Previously read: "The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the investigator. A second informed consent form (ICF) will be obtained from all medium and active-placebo dose subjects who elect to go through the open-label Stage 2 process."

Now reads: "The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the investigator."

Rationale: The protocol clarifies that a single consent form shall be used for this study, and that signing this form indicates willingness to take part in Stage 2.

Change 18: Section 13.2, "Costs to Participants," p. 49, first paragraph in section.

Previously read: "There will be no costs to the study participants. The sponsor will cover all costs of study participation."

Now reads: "There will be no costs to the study participants. The sponsor will cover all costs of study participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation."

Rationale: The protocol clearly states that the costs of any additional assessments performed solely to establish study eligibility, as stress tests or carotid ultrasound for people with controlled hypertension, will be covered by the sponsor.

Change 19: Appendix A, "Risk Mitigation," p. 63, previously no text, ninth through 12th paragraphs under "Psychological Distress,"

Previosly read: Not present.

Now reads: "The investigators have developed a contingency plan for responding to suicidal intent. They will evaluate the degree of suicidal intent and take steps to alleviate psychological distress.

Seriousness of suicidal intent would first be evaluated by the investigators both clinically and through administrations of the CSSRS. Depending upon what is learned from evaluation, the investigator might increase support for and discussion with the participant, increase frequency of contact, or if during an experimental session, remain with the subject. Hospitalization would be considered in some situations as described in Appendix A on p. 61.

If the participant exhibits signs of suicidality the investigators will also call the contact person designated by the subject."

The investigators will use the same procedures for all participants whether they are within or beyond reasonable driving distance from the study site. Increased telephone contact could be used if additional appointments were not a viable option for a participant not within easy driving distance of the site. The treating therapist of any participant living outside reasonable driving distance would be enlisted to provide evaluation and support for the participant.

Rationale: The protocol describes a contingency plan addressing participant suicidal intent.