To:    Dr. John Patrick Stewart

From:    Dr. B. Wiatrowska

Date: 22/01/2009

Security – Classification: HC Protected

Subject: Protocol Safety and Efficacy Assessment Template
Clinical Trial Application – Evaluation Report
Effective Date: 2008-03-01

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**MANAGER**

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Manager’s Signature

Canada
1. INTRODUCTION
(Information to be included in this section can be extracted from the PSEAT prepared by the sponsor)

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2. INVESTIGATOR'S BROCHURE
(The relevant sections should be filled using a check mark)

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<td>Rationale for Drug Development</td>
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3. PROTOCOL SUMMARY
(Information to be included in this section can be extracted from the PSEAT prepared by the sponsor)

Study Synopsis
A Randomized, Active Placebo-controlled Pilot Study of 3,4-
methyleneoxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects
with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada
Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
Study Number: MP-4
Principal Investigator: Ingrid Pacey MB BS FRCP[C]
Co-Investigator and Sub-Investigator: Andrew Feldmar MA; Karen Tallman PhD
Expected Study Dates Jan 2009-April 2010
Approved by: IRB Services, BC Committee, November 5, 2008

Background and Rationale

Background: This proposed Canadian pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve patients with treatment-resistant posttraumatic stress disorder (PTSD). PTSD is a debilitating psychiatric disorder that arises after a personally threatening life-event. PTSD can severely reduce quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. PTSD affects an estimated 8% of the general population at some point during their lifetime [1], as reported in a national survey of mental disorders in the general population of the US. To date the treatment of PTSD has primarily been psychotherapeutic, the effect size for psychotherapy being higher than for psychopharmacologic treatment.

Cognitive behavioral therapy is considered one of the most effective psychotherapies. Other methods such as psychodynamic therapy and eye-movement desensitization and reprocessing (EMDR) also proved to be effective in treating some aspects of PTSD symptoms [2]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [3]. A recent meta-analysis concluded that all "bona fide" psychotherapies, including all those listed above, are similarly effective with PTSD [4]. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies [5, 6], and at least one study of the selective serotonin uptake inhibitor paroxetine, approved by the FDA in the treatment of PTSD, indicated that men did not respond to this drug [7]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with 3,4-methylenedioxymethamphetamine (MDMA), a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy.

MDMA is a ring-substituted phenethylamine that bears structural and pharmacological similarities to amphetamines and the psychedelic compound mescaline. However, it possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients [8-11]. MDMA was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s [12, 13]. In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was placed in Schedule 1 in 1985 as a result of
extensive non-medical use [10, 14, 15]. Placement in Schedule 1 prohibited it for use except in a federally-approved research setting. There has been no evidence of significant or lasting toxicity in more than 400 subjects participating in Phase I or Phase 2 studies of MDMA conducted in the US, Israel, the Netherlands, Spain, and Switzerland. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens [e.g., 16, 17, 18] and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs [19-22]. In contrast, all available Phase I and Phase 2 data indicate that it is unlikely that the MDMA exposures proposed in this protocol will cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Recent retrospective and prospective studies suggest that receiving MDMA in a controlled, therapeutic setting bears little to no attendant risks of serotonin system neurotoxicity or of functional consequences of this possible toxicity. 

Rationale: Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [8, 9, 23, 24]. Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can "reduce or somehow eliminate fear of a perceived threat to one's emotional integrity" [8]. Elimination of these "conditioned fear responses" can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience [8]. Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens [25]. The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others. Though the psychopharmacology and neuropsychological underpinnings of the therapeutic effects of MDMA are largely unknown at present, Gamma and colleagues found that MDMA reduced activity in the left amygdala [26], suggesting reduced responsiveness to anxiety or fear-provoking stimuli. Preliminary data from a MAPS-sponsored study conducted in the US by Mithoefer and
colleagues are promising, suggesting significant improvements in PTSD symptoms after MDMA-assisted psychotherapy [27]. This study employed the Clinical Administered PTSD Scale (CAPS) as the primary outcome measure, with PTSD symptoms measured by a blinded, independent assessor at baseline, a week after each experimental (MDMA or placebo) session, and two months after the final experimental session. To date, all participants in this study have tolerated MDMA, and preliminary data indicates that MDMA is associated with greater improvement in PTSD than placebo. A recent analysis conducted by the independent rater detected a significant decline in CAPS score in the MDMA condition when compared with placebo [28]. A one-year+ follow-up study is currently underway.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to be an innovative treatment for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are greatly outweighed by the possibility that this treatment may offer significant benefits.

**Trial Objectives**

**Primary Efficacy and Safety Objectives:** The primary objective of this study is to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with treatment-resistant PTSD. Symptoms of PTSD will be assessed via Clinician-Administered PTSD Scale (CAPS). The Posttraumatic Diagnostic Scale (PDS) will be used as a secondary measure of PTSD symptoms. The investigators compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) session.

The investigators will also gather information on physiological effects and side effects after MDMA.

**Secondary Objectives:** The secondary objective of this study is to investigate the effects of MDMA-assisted psychotherapy on symptoms of depression in people with PTSD. Depression will be assessed via the Beck Depression Inventory (BDI). The investigators will compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

**Study Design and Duration**

The proposed pilot study will employ a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female cotherapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session.
on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. Symptoms of PTSD and depression will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment. Participants in the active placebo condition will have the opportunity to enroll in an open-label study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD and depression symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety. The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion. The randomized, double-blind, active-placebo controlled study segment will last approximately four months from screening and baseline evaluation up until the evaluation six weeks after the third experimental session. The open-label study segment for participants assigned to active placebo will last an additional four months from the single introductory and review psychotherapy session to the evaluation six weeks after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

**Number of Centres**

The study will take place at one location in Vancouver, BC. All psychotherapy, including both non-drug and MDMA-assisted sessions, will take place at the offices of the principal investigator, Dr. Ingrid Pacey. Assessments of PTSD symptoms and neurocognitive function will be performed in this office located in the same building as

**List of Investigators**
Ingrid Pacey MBBS FRCP[C] is the principal investigator for this study. She is a practicing psychiatrist in Vancouver, BC. She has worked as a psychiatrist for 36 years. She has a private practice in Vancouver, BC. She has performed Holotropic Breathwork, a therapeutic breathing practice capable of producing alterations in consciousness, in people with PTSD. She will be present during every psychotherapy session, including each experimental or open-label MDMA-assisted psychotherapy session.

Other investigators will be Andrew Feldmar M.A. and Karen Tallman PhD. Andrew Feldmar, M.A., has practiced psychotherapy as a psychologist for almost 40 years in Vancouver, Canada. He has given workshops, lectures and seminars on psychotherapy and topics of psychotherapeutic interest. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. He will be present during every psychotherapy session, including each experimental and open-label MDMA-assisted psychotherapy session. Karen Tallman Ph.D will be the independent rater who will assess participant symptoms and neurocognitive function. She is a clinical psychologist who has 15 years of experience and has conducted psychiatric diagnostic and competency assessments.

Sample Size
The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)
The investigators will seek to enroll individuals diagnosed with PTSD who score 50 or higher on the Clinician-Administered PTSD Scale (CAPS). The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all the inclusion criteria listed below without meeting any exclusion criteria. Participants must reside in Canada.

Inclusion Criteria
Participants who meet the following criteria will be considered for inclusion in this study:
1. Participants must meet DSM IV criteria for current PTSD. They must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
2. They must either:
   a. have had at least one unsuccessful attempt at treatment with a selective serotonin uptake inhibitor (SSRI) and one unsuccessful treatment with any form of psychotherapy for which there exist 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 eye movement desensitization (EMDR) [5, 29-31]. Treatment with an SSRI must have lasted for at least three months, or the participant must have refused to take SSRIs. Psychotherapy must have lasted for six months and included at least twelve sessions. Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.
   b. Be a veteran with PTSD symptoms that have persisted for no less than one year but no more than five years.
3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of subjects with other mood and anxiety disorders is essential because there is marked frequency of co-existence of other psychiatric disorders among people with PTSD [32, 33].

4. Participants must be willing to commit to medication dosing, experimental sessions, and follow-up sessions and to complete evaluation instruments.

5. 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. If they are being treated with psychoactive drugs at the time they are recruited into the study, the prospective participant will be encouraged to discuss medication withdrawal with his or her outside treating physician, and will be required to give Dr. Pacey permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA/placebo session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life). No new medications may be started until after the evaluation session, which will occur six weeks after the third experimental session. An exception to this may arise in the case of designated rescue medication that may be administered in the event of a crisis during or after the experimental session.

6. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. They must sign a release if they want to permit 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 six weeks after the third experimental session.

7. Participants must agree that, for one week preceding each MDMA/placebo session:
   a. They will refrain from taking any herbal supplement (except with prior approval of the research team).
   b. They will not take any nonprescription medications (with the exception of nonsteroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
   c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).

8. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.

9. Participants must be willing to remain overnight at after each experimental session until the non-drug session occurring the next morning. An attendant will be present to assist with personal needs if requested and offer dinner and breakfast. The attendant will be an individual with previous training in
managing psychological distress, including distress occurring after use of psychedelic drugs and of the same sex as the participant, and he or she will be trained for assisting in this study. The attendant may be anyone with some training or background in health care, particularly in psychiatric health care. The attendant will be instructed to contact Dr. Pacey at the request of the participant or if there are signs that the participant is under physical or psychological distress. At the participant’s request and with Dr. Pacey’s approval, a significant other can remain with the participant for support between the end of the experimental session and the non-drug session the next morning.

10. Participants will be asked to locate an individual willing to drive them home the morning after the experimental sessions, after the non-drug therapy session. If a participant is unable to locate someone to transport them home, the investigators will assist the participant in obtaining transport from the clinic to the participant’s home or any other location where he or she is staying temporarily.

11. Participants must be willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.

12. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.

13. Participants must be literate. They must be proficient in reading documents written in English.

Exclusion Criteria
Prospective participants will be excluded from the study if they have the following conditions or characteristics:

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.

2. People with a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.

3. People with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.

4. People with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).

5. People with hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions [34], peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.

6. People weighing less than 48 kg

7. People with prior use of "Ecstasy" (illicit drug preparations purported to contain MDMA) more than 5 times or at any time within the previous 6 months.

8. People who would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, with suicide risk ascertained via face to face interview and and through the use of the Adult Suicidal Ideation Questionnaire (ASIQ).

9. People requiring ongoing concomitant therapy with a psychotropic drug.
10. People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 6 months.
11. Any person who is not able to give adequate informed consent.

**Drug Formulation**
Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg. MDMA will be obtained from Lipomed AG. Active placebo doses of MDMA will also contain the inactive substance lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

**Dosing Regimen**
The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental condition are identical to those in use in other MAPS-supported studies of MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy performed prior to the scheduling of MDMA in the US [14, 27, 35]. The supplemental dose is also identical to the one used in the US study. The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective effects without producing physiological effects any greater than peak effects occurring after the initial dose.
Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects [36, 37] and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is expected to produce slight alterations in consciousness, as slight increases in tension or relaxation, but without producing a significant reduction in anxiety or a significant increase in access to emotionally upsetting material [37].
As described above, capsules containing the initial dose of MDMA will be administered at approximately 10:00 AM. Supplemental doses will be administered upon mutual agreement by the investigators and participant one and a half to two and a half hours after the initial dose. There will be no take-home doses. The investigators may decide not to administer the supplemental dose of MDMA if they believe that the participant exhibits signs or symptoms suggesting that an additional dose of MDMA could produce a serious adverse event.
There will not be any changes in dose regimen across the three MDMA-assisted sessions.
If the participant experienced hypertension that required clinical intervention or had a serious adverse event during an experimental session, then no further doses of MDMA will be administered.

**Washout Period**
Participants taking psychiatric medications will undergo a medication-appropriate washout period beginning upon study entry and lasting for at least five times the medication half-life before an experimental session. Participants who undergo medication...
washout will have PTSD and depression symptoms assessed again after completing the washout. This is to ensure that an appropriate comparison will be made between baseline symptoms of PTSD and symptoms six weeks after the third experimental session, when individuals will be medication-free. The first experimental session cannot occur until after a participant has completed medication washout.

**Pre-study Screening and Baseline Evaluation**

Participants will undergo medical and psychiatric screening after giving written informed consent to take part in the study. Screening will include medical history and physical examination, psychiatric interview, including administration of the SCID, for diagnosis of included and excluded psychiatric disorders, assessment of suicide risk via face to face interview and assessment with the ASIQ, urinary drug and pregnancy screening, and baseline CAPS administration by the independent rater. Medical screening will also include a blood draw for performance of standard laboratory measures of liver function, thyroid function and metabolism, and an electrocardiogram to assess heart function. The independent rater will administer the CAPS after undergoing medical and psychiatric examinations. If participants continue to meet all study criteria without meeting any exclusionary criteria, they will be enrolled in the study.

Upon enrollment, participants will undergo baseline evaluation. CAPS, PDS and BDI scores from screening evaluation will serve as baseline measures of symptoms of PTSD and depression in all cases except those of participants who underwent screening while still taking psychiatric medication, as described above.

Upon enrollment into the study, each participant will be randomly assigned to one of two conditions, active placebo or experimental dose. Each participant has a 66.6% chance of assignment to the experimental dose condition and a 33.3% of assignment to the active placebo condition. This study will employ a blinded adaptive randomization procedure in order to maintain the 66%/33% 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, and this individual will have charge of maintaining randomization procedures. A randomization list will be run to assign random numbers from one to 100 and either experimental dose or active placebo dose MDMA (125 and 62.5 or 25 and 12.5 mg) MDMA to 12 prescription bottles. The investigators will contact the randomization monitor after enrolling a participant, and the randomization monitor will select a number from amongst the set of 12 numbers, represented as cards or other indicators, thus providing 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, as when pharmacological intervention is necessary, the blind may be broken.
for an individual participant.

**Treatment Visits**

After baseline assessment, the study will consist of twelve 60 to 90 minute "conventional" or non-drug augmented psychotherapy sessions and three experimental sessions of MDMA-assisted psychotherapy, and two assessments of symptoms of PTSD and depression. The investigators will break the blind individually for each participant after the assessments six weeks after the third experimental session. Participants who learn they are assigned to active placebo can enroll in the open-label study segment. The sequence of events and procedures in Stage 2 is nearly identical to that of Stage 1 except that participants undergo one and not three introductory psychotherapy sessions and all three MDMA-assisted psychotherapy sessions are open label.

**Psychotherapy:** Study participants will receive conventional “talk therapy” before and after undergoing each experimental therapy session. They will receive three experimental psychotherapy sessions scheduled at three to five week intervals. Each experimental session will be followed by conventional psychotherapy, including psychotherapy on the morning of the day after the experimental session and two more sessions afterwards.

**Introductory Psychotherapy:** All psychotherapy will take place prior to undergoing MDMA-assisted psychotherapy, participants will have three 60 to 90 minute long introductory psychotherapy sessions, during which they will meet with the male and female co-therapist team. Participants receive introductory psychotherapy to build a working alliance with the therapists and to prepare them for the experimental psychotherapy sessions.

**Experimental Sessions:** All participants will receive three double-blind experimental sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Each experimental session will last approximately eight hours. Experimental sessions will be conducted by the male and female co-therapist team. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions, and all procedures except drug dose will be the same for participants assigned to the full dose and active placebo condition.

Participants will arrive approximately one hour before drug administration for collection of a urine specimen for drug and pregnancy screening. If drug screening results are negative and pregnancy test is negative or not applicable and the participant reports that he/she followed appropriate rules and restrictions, then the session will proceed. Before administering MDMA, the therapists and participant will discuss and review the participant’s goals, intentions and concerns and some of the commonly experienced effects of MDMA. Participants will complete the Subjective Units of Distress (SUD), a single-item measure of degree of psychological distress, just prior to initial dose administration. At approximately 10:00 AM, participants will receive the initial dose of MDMA along with a glass of water. The initial dose will either be 25 or 125 mg MDMA in accordance with condition assignment, and the dose will be administered in a double-blind manner. The supplemental dose will always be one half (1/2) the initial dose and will be administered between 1.5 and 2.5 hours after the initial
Time and Events for Randomized Study segment

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<td>Administer vMOMA X X</td>
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<td>Unblinding X</td>
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<td>Consent for Stage II-randomized X</td>
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<td>vMOMA X</td>
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<td>End Randomized phase X</td>
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<td>Independent Assessor</td>
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Time and Events for Open-Label Study Segment after Randomized Study for Active Placebo Participants

| Type of Visit Consent "Baseline" |
| Renewe/Intro Therapy |
| Open-Label 1 Integrative Therapy6 Integrative Therapy9 Integrative Therapy10 Integrative Therapy12 Integrative Therapy13 Integrative Therapy14 |
| Open-Label 2 Integrative therapy1 Integrative Therapy11 Integrative Therapy12 Integrative Therapy13 Open Label 3 Integrative Therapy14 |

**Drug Product Name:** [Proprietary Name]  
**Sponsor:** [Sponsor name]
After the session begins, participants will lie or recline in a comfortable position with eyes closed or wearing eyeshades if preferred. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material [38-40]. Throughout the duration of this session, the therapists will support and encourage the participant in emotional processing and resolution of emerging memories, thoughts or feelings. The therapist-investigators will also encourage periods of time in which the
participant remains silent, focusing attention inward, in order to allow for the further unfolding of their inner experience. Water and electrolyte-containing beverages will be available for participant consumption, and food will be offered later on in the session. Blood pressure and pulse will be measured at the outset of each experimental session and once every thirty minutes (0.5 hour) for the duration of the experimental session, with more frequent measures taken only if the established thresholds for normal blood pressure and pulse have not been exceeded. The investigators will measure participant body temperature via tympanic thermometer every 60 to 90 minutes. SUDs will be every 60 to 90 minutes until the session is over. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process, and if necessary, the investigators can make a greater number of measurements. Approximately 1.5 to 2.5 hours after the initial dose, the therapist-investigators will offer the participant the supplemental dose of MDMA. They will only do so if, in their judgment, the participant does not show any signs or symptoms suggesting that an additional dose of MDMA could produce a serious adverse event.

With the permission of the therapists, a significant other, such as a spouse, relative or close friend, may join the participant during the experimental session or at some point after it has ended. The therapist-investigators and participant will discuss the issue of having a significant other present prior to permitting a significant other to accompany the participant. If all medical parameters are acceptable and the subject is alert, ambulatory and emotionally stable, the session will end. The investigators will depart the site when they have concluded that the participant is emotionally and medically stable. Both therapist-investigators reside and can quickly return to the site if necessary. Throughout the study, at least one of the therapist-investigators will remain available to participants via 24-hour cellular phone.

Participants will remain overnight in an appropriately furnished room. With prior approval, a significant other may accompany the participant during the overnight stay. A same-sex attendant will remain with the participant during the overnight stay, even if a significant other is present. The attendant will monitor participant health and will help participants relax during the overnight stay. The attendant will be anyone with training or background in health care, particularly psychiatric health care with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs. If there is an emergency or the participant needs additional support, the attendant can contact the investigators. Starting on the day of the non-drug psychotherapy session following each experimental session, one of the investigators will contact the participant via telephone on a daily basis for one week.

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Drug Product Name: [Proprietary Name] 15 Sponsor: [Sponsor name]
Integrative Psychotherapy: Participants will undergo non-drug psychotherapy on the day after each MDMA-assisted session and on a weekly basis during intervals after and between each MDMA-assisted session. During these 60 to 90 minute psychotherapy sessions, the participant and therapists will work to integrate material from experimental sessions into the participant's everyday life.

An integrative psychotherapy session will take place on the morning of the day after each experimental psychotherapy session. The participant and investigator will discuss and review events, thoughts, feelings and memories that occurred during the experimental session. If necessary, the therapist-investigators will help the participant to reduce any residual psychological distress he or she is experiencing. Participant and investigator beliefs about participant condition assignment will be assessed on the morning of the day after each experimental session. After this psychotherapy session, a person previously selected by the subject will provide a ride home. The investigators will help secure a ride home for participants who are unable to locate a ride.

The participant will meet with the therapist for at least two more integrative psychotherapy sessions to be scheduled between experimental sessions or after the third and final experimental session. The participant and investigators will continue to work on supporting the participant as she or he considers his or her experiences during experimental sessions. The investigators may arrange to work on reducing the distress at a specially scheduled non-drug therapy session, through continuing contact, or at the next regularly scheduled non-drug therapy session. The participant may also initiate contact with the investigators at any time throughout the study. There will be no more visits for approximately one month between integrative psychotherapy after the third experimental session and assessment six weeks after the third experimental session.

Evaluation Six Weeks After the Third Experimental Session: The final evaluation in the double-blind portion of the study will occur six weeks after the third experimental session. Participants will meet the independent rater for a 90 to 120 minute evaluation wherein the independent rater will administer the CAPS and participants will complete the BDI and PDS. The independent rater will also administer the RBANS and PASAT.

Unblinding and Opportunity for Participants in Active Placebo Condition Enroll in Open-Label Study Segment ("Stage 2"): After undergoing assessment of symptoms of PTSD and depression with the independent rater, the blind will be broken for the therapist-investigators and the participant, with the independent rater remaining blind to condition assignment. During this 30 to 60 minute meeting, the investigators will provide consent materials for the open-label study segment to participants assigned to the active placebo condition. These participants who elect to enroll in stage 2 will undergo a course
of therapy and evaluation nearly identical to the randomized study, but with experimental
dose MDMA given in an open-label context. They must give written, informed consent
before enrolling in the open-label study segment.
Assessment of PTSD symptoms and depression six weeks after the third experimental
session will serve as baseline assessments for comparison with assessments made after
final open-label sessions except in the case of people who begin open-label sessions more
than thirty days afterwards. In that case, the independent rater will re-administer the
CAPS, PDS and BDI, and these scores will serve instead as baseline for comparison to
assessment after final open-label session.
Participants who are not continuing on to the open-label study segment will complete the
Reactions to Research Participation Questionnaire (RRPQ), a measure of experience as a
research participant.
Open-Label Study Segment for Active Placebo Participants ("Stage 2"): Participants
assigned to active placebo during the randomized study segment will undergo three
open-label
MDMA-assisted therapy sessions that follow a course and schedule similar to the randomized study except that participants undergo one instead of three introductory
sessions. After giving written informed consent, participants enrolled in Stage 2 will meet
with both therapist-investigators for a single review and re-introductory psychotherapy
session, followed by an open-label MDMA-assisted therapy session. Participants will have the same sequence of integrative therapy and open-label sessions scheduled three to
five weeks apart.
All participants in Stage 2 will be assessed by the independent rater six weeks after the third, final open-label session. The independent rater will assess all participants on the
CAPS and participants will complete the PDS and BDI, and RRPQ.
Audio and Video Recording: All sessions from introductory psychotherapy through
weekly integrative psychotherapy and including experimental and open-label
MDMA-assisted
sessions, will be recorded to audio and video in their entirety. These recordings will be used for further analysis of patient behaviour, defense mechanisms, and therapist
interventions and for development of a manual of standard procedures for performing
MDMA-assisted psychotherapy in people with PTSD.
Premature Withdrawal/Discontinuation Criteria
The participant, or where applicable, the participant's legally acceptable representative(s)
can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best
interest of the subject or if the subject cannot comply with the protocol. Cause for
withdrawal from the study include, but is not limited to, positive urinary pregnancy screen, positive urinary drug screen, drug-related adverse event requiring hospitalization or immediate clinical intervention (as high, sustained elevation in blood pressure, elevated body temperature, psychotic reaction), signs of liver disease, and signs of sustained impaired cognitive function, resumption of psychiatric medication for another condition, or failure to follow investigator instructions. Failure to follow one or more instruction related to pre-session food or beverage consumption may lead to delaying experimental or open-label session start time, rescheduling the session or withdrawing the participant from the study.

Rescue Medication and Risk Management

Approximately 390 people have received MDMA during controlled trials without the occurrence of any drug-related serious adverse event, and psychiatrists in the US and Europe reported administering MDMA to at least a thousand patients before the drug was made illegal without any occurrence of drug-related serious adverse events [9, 11, 14, 41]. MDMA side effects include loss of appetite, dry mouth, impaired concentration, impaired gait or balance and tight jaw muscles, and fatigue lasting for up to two days afterwards [37, 42-46]. Increased anxiety, mild perceptual alterations (as colors seeming brighter) and increased anxiety are reported in clinical trials [35, 37, 46-48]. Approximately 5% of study participants exhibit clinically significant elevation in blood pressure, none requiring clinical intervention [46, 49].

Currently there is no known antidote to MDMA. There are pharmacological or psychotherapeutic treatments for specific effects of MDMA. Anti-hypertensives can be used to reduce elevated blood pressure. Supportive care can be used in response to anxiety or panic reactions. Benzodiazepines could also be used in response to panic reactions or psychotic responses. Human drug co-administration studies suggest that conventional (first generation) anti-psychotics will not reduce, and may even increase, anxiety after MDMA [44]. It is possible but currently uncertain, that serotonergic antipsychotics, such as olanzapine, could be used to treat psychotic response to MDMA.

The investigators will not administer a subsequent dose of MDMA if an individual exhibits a severe panic response or signs of liver disease, and they may decide not to administer a subsequent dose of MDMA after elevation in blood pressure that required clinical intervention.

Serious adverse effects of ecstasy (material represented as MDMA) are rare even outside controlled settings [50]. In uncontrolled settings, hyperthermia is the most common of these events [42, 51]. In addition to hyperthermic syndromes, other rare adverse events include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia. Hypertension and Cardiovascular Effects: Participants with hypertension, cardiovascular, coronary, pulmonary or cerebrovascular disease will be excluded from study participation. The investigators will address the cardiovascular effects of MDMA through
periodically monitoring blood pressure and pulse at regular 30-minute intervals. If at any
time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110,
measurements will be taken every 5 minutes until the values fall below these levels or
until they have been decreasing for 15 minutes or have stabilized at a level judged by
the
investigator to be safe. The investigators may send the participant to an emergency
department if they judge it necessary to do so.

Psychological Distress: Preparation for each experimental or open-label session and
supportive care during each session will be used to address and potentially reduce
psychological distress. Participants with psychiatric conditions that place them at
increased risk of psychosis, such as past or current psychotic disorders or dissociative
identity disorder, will be excluded from study participation. Preparation will include
discussing what might occur during an MDMA-assisted therapy session and teaching
techniques such as diaphragmatic breathing. The investigators will explain to
participants
that anxiety will not be treated pharmacologically during the sessions because anxiety
presents an opportunity to therapeutically address the symptoms and underlying causes
of
PTSD. Every effort will be made to help participants move through difficult emotions
and arrive at a more comfortable and relaxed state by the conclusion of the session. In
the event that a participant is experiencing severe emotional distress, such as panic
attacks, severe generalized anxiety or insomnia, following an experimental session, the
principal investigator may prescribe a benzodiazepine or other anxiolytic drug, as
zolpidem. The investigators may remain with the participant until they believe that he or
she is stable, and they have the option to hospitalize any participant who may be in
danger of harming him or herself or others.

Hyperthermia: The investigators will address risk of hyperthermia by assessing body
temperature every 60 to 90 minutes with a tympanic thermometer. If temperature rises
more than 1 ° C, attempts will be made to lower it by removing blankets and layers of
clothing, decreasing ambient temperature and, if necessary, directing a fan toward the
participant. If at any time the temperature rises more than 1.5° C above baseline despite
these efforts, the investigators will consult by telephone with a physician at the nearest
emergency room to discuss whether the subject should be transported for further
evaluation. If the temperature continues to rise, or if an elevated temperature is
associated
with delirium or muscle rigidity paramedics will be summoned to stabilize and transport
the subject to a nearby emergency department.

Hypnatremia: Electrolyte solutions such as Gatorade will be available throughout each
experimental or open-label session. Participants will not be allowed to drink more than 3
L. of fluids over the course of the experimental session, and fluid intake will be spread
out appropriately during the session. The investigators will ensure adequate fluid intake
by encouraging the subject to drink electrolyte solution or water at least hourly if
subjects
are not doing so spontaneously. If there are any signs or symptoms of hyponatremia
such
as confusion, vomiting, myoclonus or ataxia, beyond mild, transient symptoms that may
be associated with MDMA effect the subject will be transported to the nearest emergency department.

*Liver Toxicity:* People with liver disease will be excluded from study participation. Participants will be monitored for signs of liver toxicity. If a participant exhibits signs of liver toxicity after an experimental session, then he or she will not receive a subsequent experimental session.

*Neuropsychological Toxicity:* Psychological and neurological status will be clinically monitored by the therapists during MDMA sessions and during therapy sessions at frequent intervals thereafter. If, on clinical examination after each experimental session, a participant is found to have cognitive deficits that persist for more than two weeks, this participant will not be given a subsequent experimental session. Cognitive function will be assessed at baseline and again six weeks after the third experimental session.

*Abuse and Dependence:* The investigators will exclude all participants meeting the criteria for substance abuse or dependence within six months prior to screening and all participants who report using ecstasy on five or more occasions or at any time in the past six months. Urine drug testing will occur before each experimental or open-label MDMA session. The researchers will be alert to the question of MDMA abuse during the treatment phase and will explicitly address this point at the closing visit.

*Receipt of Active Placebo:* As part of the active-placebo controlled study design, four of twelve participants will receive active placebo doses of MDMA during MDMA-assisted psychotherapy instead of experimental doses. Participants who receive active placebo dose MDMA during the randomized study segment will have the opportunity to undergo three open-label MDMA-assisted sessions in Stage 2.

*Concomitant Medication*

Participants are not allowed to take any psychiatric medications throughout the course of the study, with the exception of gabapentin for pain management. This includes antidepressants, anti-anxiety medication and antipsychotics. For one week preceding each experimental or open-label MDMA-assisted psychotherapy session and by extension including the entire day of the experimental or open-label session, participants may not take any herbal supplement, nonprescription or prescription medication except any supplement or medication that the investigator has reviewed and given prior approval for use. However, participants may take these medications at all other times during the study. Medications allowed throughout the study include birth control pills, non-steroidal antiinflammatory medication (as aspirin, ibuprofen), acetaminophen and thyroid hormones. Specific anxiolytics, as benzodiazepines, may be administered to treat insomnia or anxiety more than 24 hours after an experimental or open-label session.

**Efficacy Variables & Analysis**
Global CAPS scores assessed six weeks after the third experimental (blinded) session will serve as the primary endpoint for assessing treatment efficacy. An independent rater who will not be present during any experimental or non-drug assisted sessions will administer the CAPS at baseline and again six weeks after the third experimental session. The CAPS provides a means to evaluate the frequency and intensity dimensions of each symptom, impact of symptoms on the patient's social and occupational functioning, overall severity of the symptom complex and global improvement since baseline and the validity of the ratings obtained. The CAPS takes approximately one hour to complete. CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [52, 53].

The primary endpoint of six weeks after the third experimental session was chosen to take place after all three experimental sessions of active placebo or experimental dose MDMA and after the participant had completed the course of psychotherapy for the study. The endpoint was also selected to make it comparable with the primary endpoint employed in earlier and ongoing sponsor-supported studies of two months after two experimental sessions. The endpoint is intended to examine the stability of response and to avoid any immediate effects of the experimental sessions. Secondary endpoints for assessing efficacy will also occur six weeks after the third experimental (blinded active placebo or experimental dose MDMA) sessions, and will include scores on the PTSD Diagnostic Scale (PDS) and assessing symptoms of depression with the Beck Depression Inventory (BDI). The PDS was designed to assess PTSD following DSM criteria [54, 55]. This 49-item self-report scale assesses degree of distress, and presence of intrusive thoughts, avoidance of situations that trigger intrusive thoughts, and hypervigilance. The PDS assesses duration of symptoms and degree of impairment. The Beck Depression Inventory (BDI) is a 21-item a self-report measure of depressive symptoms [56, 57] that will serve as a measure of depression. It takes five to ten minutes to complete.

PTSD and depression symptoms will be assessed in people enrolled in the open-label Stage 2 study segment six weeks after the third open-label session in order to compare PTSD symptoms at the start of the study, after receiving active-placebo dose MDMA and after experimental-dose MDMA.

The final endpoint for assessing neurocognitive function after active-placebo or experimental dose MDMA-assisted psychotherapy will also occur six weeks after the third experimental session, with scores at this time compared with baseline performance.

The RBANS, a battery of neurocognitive tests [58] and the PASAT, a measure of information processing speed and efficiency [59] will all be administered at these two time points. The RBANS is used to support the broad-based assessment of multiple cognitive domains with index scores for immediate memory, visuospatial/constructional, language, attention, and delayed memory. The PASAT is a sensitive measure of...
information-processing speed and efficiency, concentration skills, and immediate memory which has an extensive literature associated with the effects of brain dysfunction.

*Laboratory Assessments:* Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. Urinary screens for drugs of abuse and pregnancy will be performed just prior to each experimental or open-label session; all other laboratory tests will be performed as part of screening for study enrollment. Tests will include assessment of thyroid and liver function. All abnormal laboratory values require a comment from the investigator on the laboratory report, regardless of the clinical significance. After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by the investigator.

*Side Effects and Adverse Events:* The investigators will record spontaneously reported side effects during and for one week after each experimental or open-label session. Adverse events that will be collected for the duration of the study include any events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions and any adverse event leading to withdrawal from the study. All serious adverse events will be collected for the duration of the study. All SAEs which occur during the course of the trial, whether considered to be associated with the study IP or not, have to be reported within 24 hours or at the latest on the following working day by telephone or fax to either the medical monitor or the sponsor study monitor.

Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data. The sponsor will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

**Statistical Analysis**

The investigators will examine the effects of active placebo versus experimental dose MDMA-assisted psychotherapy on symptoms of PTSD as assessed via CAPS global scores by conducting between subjects / within-subjects analyses of variance (ANOVA) with condition (active placebo versus experimental dose) as a between-subjects variable and time of administration (baseline versus six weeks after third experimental session) as a repeated measure. The investigators will perform post-hoc tests on any interaction and probability of rejecting the null hypothesis will be set at 0.05. If there is a significant interaction between condition and time of administration, the investigators will perform separate between-subjects / within-subjects ANOVAs on CAPS sub-scale scores to
examine whether any facet of PTSD symptoms is particularly affected by
MDMA-assisted
psychotherapy. The investigators will perform the same analyses upon PDS
scores.
The investigators will perform a correlational analysis examining possible relationships
between symptoms of PTSD and depression by correlating CAPS global scores and
BDI
scores at each time of administration, with the probability of rejecting the null hypothesis
set at 0.05, and by correlating PDS and BDI scores at each time of administration.
The investigators will examine the effects of psychotherapy combined active placebo
versus experimental dose MDMA on symptoms of depression, measured by BDI
scores,
by performing a between-subjects / within-subjects ANOVA with condition (active
placebo versus experimental dose) as a between-subjects factor and time of
administration (baseline versus six weeks after the third experimental session) as a
repeated measure.
The investigators will further examine the effects of MDMA-assisted psychotherapy on
symptoms of PTSD and depression by comparing symptoms after experimental and
open-label sessions. The investigators will perform repeated-measures ANOVAs
comparing CAPS, PDS and BDI scores at randomized study baseline and six weeks
after
the third open label session, with time of administration as a within-subjects factor and
with p. set at 0.05. They will perform one analysis comparing CAPS, PDS and BDI
scores after experimental and open-label sessions for participants in the experimental
condition and another analysis for participants enrolled in “Stage 2.”
The investigators will examine the effects of MDMA on neurocognitive function by
performing a between-subjects / within-subjects ANOVA with condition as a
between-subjects
factor (active placebo versus experimental dose MDMA) and with time of
administration (baseline, six weeks after the third double-blind session) as a
within-subjects
factor and with p. set at 0.05. Participant scores on the RBANS and PASAT will
be compared at both times.
Safety of MDMA-administered psychotherapy will be assessed by performing
descriptive
statistics of vital signs and subjective distress during each experimental or open-label
session. The investigators will informally or formally compare peak blood pressure,
heart
rate and body temperature for participants after sessions using 125 and 150 mg MDMA,
depending upon the number of times, if any, the investigators administer 150 mg during
the study.
References
2. Ursano, R.J., et al., Practice guideline for the treatment of patients with acute
Protocol Synopsis 24 MAPS Study: MP-4
Pl: Ingrid Pacey


2761-88.
51. Williams, H., et al., "Saturday night fever": ecstasy related problems in a London
Protocol Synopsis 27 MAPS Study: MP-4
Pl: Ingrid Pacey

4. INFORMED CONSENT FORM
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5. OVERALL ASSESSMENT

Current Problems/Concerns:

Response to Clarifax t: control #126833, sent as electronic mail
Sent to Rick Doblin on January 16, 2009 from Beata Wiatrowska, M.D., FRCP(C)

1. Please provide updated information on studies of MDMA-assisted psychotherapy for PTSD and/or for potentially life threatening illness, if available.

All 21 participants in the MAPS-sponsored US study of MDMA-assisted psychotherapy in people with PTSD have completed the study. A long-term follow-up will soon be launched. A
preliminary data analysis found a greater decrease in PTSD symptoms after MDMA-assisted psychotherapy than after psychotherapy and inactive placebo. No drug-related serious adverse events (SAEs) occurred during this study. As of January 20, 2009, the MAPS-sponsored Swiss study of MDMA-assisted psychotherapy in people with PTSD has completed treatment of ten of twelve subjects. The eleventh subject has just been enrolled, and a potential twelfth and final subject is in the screening process. The MAPS-sponsored MDMA/PTSD study in Israel has so far completed treating two subjects and has enrolled a third subject. The second subject had PTSD for over 40 years, from the 1967 “Six Day” War, and after treatment has very few symptoms. No drug-related serious adverse events occurred during either the Swiss or Israeli MDMA/PTSD studies.

The study of MDMA-assisted psychotherapy in people with anxiety associated with advanced-stage cancer, conducted at McLean Hospital, Harvard Medical School, has enrolled one participant. This subject had a remarkably successful outcome in terms of reduced anxiety and pain and reported enhanced communications with his family.

2. Please provide more detailed reasons for the Swiss Government revoking permission to conduct MDMA assisted psychotherapy.

In 1988, the Swiss Ministry of Health gave permission to a small group of Swiss psychiatrists (members of the Swiss Medical Society for Psycholytic Therapy-SAEPT) to administer MDMA and lysergic acid diethylamide (LSD) to their Swiss patients within a psychotherapeutic context. Permission was revoked in 1993, for reasons completely unrelated to the administration of MDMA or LSD in psychotherapy.

The Swiss Ministry of Health revoked permission after one of the Swiss psychiatrists conducted a group psychedelic therapy session in France, where he had no permit to do so. During the group session, he administered different psychedelic substances to different participants. Tragically, one of the participants in this event died after receiving the psychedelic compound ibogaine (not administered in combination with any other drug). The Swiss government subsequently closed the Swiss program in which LSD and MDMA were permitted to be used in patients, at first temporarily and then permanently. A brief account of these events can be found in the attached letter from Swiss psychiatrist Dr. Peter Gasser, President of SAEPT.

3. a) What is the abuse/addiction potential of MDMA?
b) What would be the estimated risk of abuse of MDMA for a participant in this trial after the completion of all MDMA-assisted psychotherapy sessions?
c) How does the abuse potential of MDMA compare to abuse potential of psychostimulants used as medications (e.g. methylphenidate, dexedrine etc.?)

   a) MDMA possesses moderate abuse liability.
   b) The estimated risk of abuse of MDMA after completing a trial of MDMA-assisted psychotherapy is very low.  is aware of one subject in his study who used MDMA after the completion of the study. Afterwards, she said she would never do that
The Drug Enforcement Administration placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use. MDMA was scheduled shortly after people started using it in non-medical settings, as nightclubs or at parties (Beck and Rosenbaum 1994). Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006). However, monkeys will “pay” higher prices in lever presses for psychostimulants than they will for MDMA (Lile et al. 2005; Wee and Woolverton 2006). Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence (Huizink et al. 2006; Lieb et al. 2002), though studies of non-representative samples have reported higher rates of dependence (Cottler et al. 2001). Most regular ecstasy users report taking ecstasy no more often than once a week (von Sydow et al. 2002). Taken together, an examination of findings in humans and nonhuman animals suggests

Abuse Liability (from p. 87)

The Drug Enforcement Administration placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use. MDMA was scheduled shortly after people started using it in non-medical settings, as nightclubs or at parties (Beck and Rosenbaum 1994). Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006). However, monkeys will “pay” higher prices in lever presses for psychostimulants than they will for MDMA (Lile et al. 2005; Wee and Woolverton 2006). Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence (Huizink et al. 2006; Lieb et al. 2002), though studies of non-representative samples have reported higher rates of dependence (Cottler et al. 2001). Most regular ecstasy users report taking ecstasy no more often than once a week (von Sydow et al. 2002). Taken together, an examination of findings in humans and nonhuman animals suggests
that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

4. Re: Inclusion criterion #2a: Please change the criterion 2a so that in addition to an unsuccessful course of appropriate psychotherapy a participant must have had at least one unsuccessful attempt at treatment with SSRI or mirtazapine or MAOI, and that treatment must have constituted an adequate trial (lasting for at least 3 months at optimal doses or the patient could not tolerate the treatment, i.e. the patients who simply refused a trial of any of the approved form of pharmacotherapy would not be eligible for this study).

We agree without reservation to expand the inclusion criteria to include people treated with pharmacotherapies other than SSRIs.

However, we believe that potential subjects who did not successfully resolve their symptoms after psychotherapy and who have refused pharmacotherapy, should continue to be enrolled in the study. People who refuse pharmacotherapy have made a legitimate decision concerning their health care and have the right to make those decisions. For those patients, it remains true that, for them, currently available treatments have not been of sufficient therapeutic efficacy.

Based on substantial evidence, risk of study participation is not large. There are no significant safety reasons to exclude patients who have failed on psychotherapy and refuse pharmacotherapy. We would prefer to continue to enroll any subjects who have failed on psychotherapy but refused pharmacotherapy.

5. Re: Inclusion criterion #2b: Please clarify that being a veteran with PTSD symptoms that have persisted for no less than 1 year but no more than 5 years would only qualify to participate in the study if this veteran also meets criterion #2a.

That is correct; all veterans must meet all criteria including #2a to be enrolled in the study. This original inclusion criteria was written in 2001, when MAPS was seeking approval for the first US MDMA/PTSD study. We would like to revise this inclusion to permit enrollment of veterans with PTSD of no more than ten years duration. This revision is proposed upon recognition that people in the US MDMA/PTSD study had PTSD for an average of 19 years before enrolling in the study and were still successfully treated, even a subject receiving disability payments. Canadian soliders with PTSD may have experienced combat-related PTSD prior to 2004, such as in Afghanistan in UN peacekeeping missions.

6. Re: Exclusion criterion #10: Please extend the time that the participant must be in remission for substance abuse or dependence (except caffeine and nicotine) to 12 months- i.e. full sustained remission, if substance abuse or dependence was an issue.
We would prefer to retain a six-month exclusion period for active substance abuse. Participation in MDMA-assisted psychotherapy reduces rather than increases the risks of substance abuse due to the focus on resolving subjects' underlying psychological issues.

Upwards of 40% of people with PTSD also report a lifetime diagnosis of alcohol or substance abuse (Brady and Sinha 2005). As noted above, the risk of abuse of MDMA within a psychotherapy context is low. The study of MDMA-assisted psychotherapy in the US excluded people reporting a diagnosis of substance abuse within 60 days, without any abuse or dependence occurring afterwards. Given the significant number of people with PTSD reporting past alcohol or substance abuse in the past and the low risk of abuse from study participation, we believe that maintaining the current six-month diagnosis exclusion will allow for greater ease of recruitment and will also result in a more representative sample being recruited.

Kathleen Brady MD, a Professor of Psychiatry at the Medical University of South Carolina and the Associate Dean for Clinical and Translational Research, an internationally recognized expert on PTSD and dual diagnosis, wrote a letter to Canadian IRB Services in support of an exclusion using the 60-day period. We agreed to a compromise and extended the exclusion to six months. We request the same compromise in our Canadian MDMA/PTSD study.

7. Re: Informed Consent:

a) Re: risks of MDMA: Please provide the percentage of people expected to experience each of the listed potential adverse effects.
b) Please clarify that people who had recently (in the last 365 rather than 60 days) problems with drug abuse should not take part in this study.
c) Please provide what is the average expected increase in blood pressure and heart rate.

a) Percentages for most commonly reported side effects range from 40% to 70%, as stated in the current ICF, while less commonly experienced effects occurred in at least 13% of participants in Phase 1 studies. Percentages can be viewed in an attached document.

Some of the findings of potential risks are derived from studies reporting inferential and not descriptive statistics, as with changes in perception and immunological effects. In these cases, exact percentages cannot be provided but are presumed to be greater than 50%.

None of the serious adverse events listed as occurring with ecstasy users have occurred in MDMA Phase I studies of over 400 people or in any of the MDMA/PTSD Phase II studies with about 36 people treated to date. We provide percentages of people likely to experience a given adverse effect if the information is available. If desired, an estimated percentage can be made from studies presenting data as inferential statistics.

b) We will clarify the IC however you require, after you have reviewed our request to retain the current exclusion of subjects with active substance abuse in the prior 6 months.
c) From previous studies of 365 people and using identical or similar doses of MDMA, average increase in SBP was 30-35 mmHg and average increase in DBP was 15-20 mmHg. Average elevation in heart rate was 18-20 beats per minute (BPM).

The cited attachments are available as a hard copy. The questions and sponsor’s responses were discussed with 

**Reviewer’s Discussion/Summary:**

<table>
<thead>
<tr>
<th>Non-Clinical and Clinical Safety &amp; Efficacy Assessment Completed:</th>
<th>Applicable</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason: [If the drug has not been reviewed previously, there is a substantial amount of new information that has not been captured in the PSEAT-CTA, or this is a new indication, the Non-clinical and Clinical Safety &amp; Efficacy Assessment should be completed as appropriate.]</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

This pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve adult patients with treatment-resistant posttraumatic stress disorder.

Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female cotherapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.

Participants in the active placebo condition will have the opportunity to enroll in an openlabel study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD and depression symptoms six weeks after the third open-label session.
Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

In the event that a participant is experiencing severe emotional distress, such as panic attacks, severe generalized anxiety or insomnia, following an experimental session, the principal investigator may prescribe a benzodiazepine or other anxiolytic drug, as zolpidem. The investigators may remain with the participant until they believe that he or she is stable, and they have the option to hospitalize any participant who may be in danger of harming him or herself or others. The investigators will not administer a subsequent dose of MDMA if an individual exhibits a severe panic response or signs of liver disease, and they may decide not to administer a subsequent dose of MDMA after elevation in blood pressure that required clinical intervention.

The investigators will address the cardiovascular effects of MDMA through periodically monitoring blood pressure and pulse at regular 30-minute intervals. If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. The investigators may send the participant to an emergency department if they judge it necessary to do so.

If there are any signs or symptoms of hyponatremia such as confusion, vomiting, myoclonus or ataxia, beyond mild, transient symptoms that may be associated with MDMA effect the subject will be transported to the nearest emergency department. The investigators will address risk of hyperthermia by assessing body temperature every 60 to 90 minutes with a tympanic thermometer. If temperature rises more than 1°C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing ambient temperature and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5°C above baseline despite these efforts, the investigators will consult by telephone with a physician at the nearest emergency room to discuss whether the subject should be transported for further evaluation. If the temperature continues to rise, or if an elevated temperature is associated with delirium or muscle rigidity paramedics will be summoned to stabilize and transport the subject to a nearby emergency department.

COMMENT:
The rationale for the proposed study of MDMA-assisted psychotherapy is sound. The study design including proposed doses of MDMA follow the previous pilot studies in US and Switzerland. Safety issues are addressed adequately. NOL is proposed for this study.
Overview

(+/-) 3,4-methylenedioxyamphetamine (MDMA, 3,4-methylenedioxy-
nmethylamphetamine, N-methyl-3,4-methylenedioxyamphetamine,) has the chemical
formula of C\textsubscript{11}H\textsubscript{15}N\textsubscript{0}2. It is a phenylisopropylamine derived from safrone, an aromatic oil
found in sassafras, nutmeg, and other plants (Shulgin 1986). Merck patented MDMA in
1912 as an intermediate chemical involved in the production of the styptic hydrastinine
(Freudenmann et al. 2006). No significant investigations examined the pharmacological,
physiological or psychological effects of MDMA until the 1950s, when the US Army
administered MDMA to guinea pigs, monkeys, mice, rats and dogs, but not humans, as
part of a military research program, possibly intended to develop chemical incapacitants
or means of enhancing interrogation (Hardman et al. 1973). While evidence exists for
intentional use of MDMA as early as the late 1960s (see Shulgin and Shulgin 1991),
and there are records of a police seizure of MDMA in the early 1970s that suggests either
intentional or unintentional use (Gaston 1972), Shulgin and Nichols were the first to
report on the effects MDMA in humans (Shulgin and Nichols 1978). Shulgin introduced
MDMA to a psychotherapist he knew, and the psychotherapist went on to introduce
MDMA as a psychotherapeutic adjunct to others, with MDMA-assisted psychotherapy
first occurring during the mid to late 1970s. Some have estimated that up to 4000
people underwent MDMA-assisted psychotherapy in North America prior to its placement in
Schedule 1. Psychotherapists used it to treat anxiety and depression, and posttraumatic
stress disorder (Greer and Tolbert 1998; Metzner and Adamson 2001).

A few uncontrolled human studies of MDMA occurred in the 1980s (Downing 1986;
Greer and Tolbert 1986), including Greer and Tolbert's study of MDMA in a
psychotherapeutic context. However, controlled human studies of MDMA did not
commence until early to mid-1990s, with the publication of research conducted by Grob
and colleagues (Grob et al. 1996). Currently, ongoing investigations in the US and
Switzerland are examining the use of MDMA in psychotherapy (Halpern 2006;
Mithoefer 2006; Oehen 2006).

Pharmacological and toxicological effects
MDMA possesses a complex pharmacological profile, but it is dominated by its effects
on monoamine release and reuptake. MDMA prevents uptake of serotonin (5-HT),
norepinephrine (NE) and dopamine (DA) and is involved in the release of these three
transmitters, with the greatest effects on serotonin release. While MDMA also has some
affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors,
strength of activity on these receptors is low (Battaglia et al. 1988; Setola et al. 2003,
see also values listed on NIMH Psychoactive Drug Screening Program). There are a few
studies of changes in gene expression seen after MDMA, but given that these studies use
Pharmacokinetics and biological disposition

MDMA is chiral, possessing two enantiomers, S-(+)-MDMA and R-(-)-MDMA, with S-(+)-MDMA is more potent than R-(-)-MDMA (Lyon et al. 1986; Shulgin 1986). Rodent drug-discrimination and behavioral studies (Fantegrossi et al. 2003; Yarosh et al. 2007) and self-administration studies in monkeys (Fantegrossi 2007), suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. One microdialysis study suggests that S-(+)-MDMA is associated with greater dopamine release in specific brain areas (Acquas et al. 2007). However, most if not all street doses are racemic, meaning they contain roughly equal amounts of both enantiomers, and all controlled studies to date also employed a racemic mixture.

The nature of differential effects of the two enantiomers of MDMA remain unknown in humans. An early uncontrolled study suggests differential effects (Anderson et al. 1978), and a controlled study comparing the enantiomers of the related compound MDE reported R-(-)-MDE to more strongly affect visual perception than the S-(+)-enantiomer (Spitzer et al. 2001).

Intravenous MDMA has an LD50 of 97 mg/kg in mice and 49 mg/kg in rats, 14 to 18 mg/kg in dogs and 22 mg/kg in monkeys (Frith et al. 1987; Hardman et al. 1973). Estimating from this data, LD50 in humans is liable to fall between 10 and 20 mg/kg (Shulgin 1986). One team of researchers reported that in mice, aggregate LD50 was 20 mg/kg, considerably lower than values in isolated animals, and recent studies in mice confirm lower LD50 when mice are housed together (Davis et al. 1987; Fantegrossi et al. 2003). Typically, human trials have used doses between 1 and 2 mg/kg.
methyleneoxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% (de la Torre et al. 2004). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

**Safety and effectiveness in humans obtained from prior clinical studies**

When Merck first patented MDMA, it was solely as an intermediate step toward the production of another compound (Freudenmann et al. 2006), and there were no early clinical investigations of MDMA. Published accounts of MDMA-assisted psychotherapy first appeared during the time of hearings for the scheduling of MDMA (Adamson 1985). Shortly afterwards, the only published study of MDMA-assisted therapy appeared, an uncontrolled study conducted in 29 individuals with mild to moderate psychiatric problems (Greer and Tolbert 1986). These accounts suggested that, when combined with psychotherapy in a supportive setting, MDMA offered benefits to people experiencing various forms of anxiety disorder, including PTSD and anxiety in association with a lifethreatening illness. The Swiss government permitted psychotherapists to conduct MDMA-assisted psychotherapy between 1988 and 1993 (Gasser 1994; Widmer 1998). These therapists reported that MDMA-assisted psychotherapy was tolerated and did not report any serious adverse events occurring after MDMA administration. The Swiss psychotherapists did not publish any formal analyses of the treatment. Permission to conduct MDMA-assisted psychotherapy in Switzerland was revoked due to events unrelated to the safety or efficacy of MDMA and due to the lack of any published research results.

Narrative accounts report that individuals experienced less anxiety and sometimes reported feelings of reconciliation with the self or others or greater positive attitudes after MDMA-assisted psychotherapy (Greer and Tolbert 1998; Metzner and Adamson 2001). A majority of the participants in the uncontrolled study of MDMA-assisted psychotherapy followed two months to two years later reported experiencing increased positive mood and more positive attitude changes since undergoing MDMA-assisted therapy (Greer and Tolbert 1986).

To date, there are four investigations underway to study the safety and efficacy of MDMA-related psychotherapy in people with PTSD and in people with anxiety arising from diagnosis with advanced-stage cancer (Halpern 2006).

**Possible Risks and Side Effects**
**Fatalities**

Fatalities have occurred after the use of MDMA or related drugs in non-medical settings (Baggott et al. 2001; Henry and Rella 2001). Ecstasy-related fatalities are rare (Baggott 2002; Gore 1999). Most are related to hyperthermia and complications arising from hyperthermia. Other causes of death include hyponatremia and cardiac events (as arrhythmias or heart attack). Some ecstasy-related fatalities may be due to reckless behavior, such as driving under the influence of ecstasy. Baggott and colleagues found that men outnumbered women in most ecstasy-related fatalities except in the case of hyponatremia, where women outnumbered men (Baggott et al. 2001). The association between MDMA/ecstasy and fatalities is generally dose-dependent, except in the case of hyponatremia-related fatalities (see for example Greene et al. 2003). At least half the ecstasy-related fatalities listed seem to involve use of other drugs (Gilhooly and Daly 2002; Raikos et al. 2002; Schifano et al. 2003).

**Common Adverse Effects and Side Effects**

Common adverse and side effects of MDMA include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001b; Mas et al. 1999). Some reports indicated decreased rather than increased alertness (Cami et al. 2000). Other common side effects reported in controlled studies of MDMA are listed in Table 2 and include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or facilitated recall (Vollenweider et al. 1998), and unusual thoughts or ideas (Harris et al. 2002). Other less common side effects include parasthesias (unusual body sensations) such as tingling sensations, or feeling hot or cold. These effects are transient and recede with the waning of drug effects. One study found that women were more likely than men to experience most commonly reported side effects of MDMA, though men were more likely than women to experience the specific side effects of nausea and sweating (Liechti et al. 2001b).

Sub-acute effects appearing 24 to 48 hours (1 to 2 days) after MDMA include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability (Baggott et al. 2001; see also Liechti et al. 2001a), with sub-acute effects waning by or within 72 hours of MDMA administration. While ecstasy users in naturalistic studies reported increased feelings of depression or aggressiveness four days after taking ecstasy (Hoshi et al. 2007a; Verheyden et al. 2003), far fewer participants in controlled studies report mood-related sub-acute effects. Naturalistic studies examining the time course of sub-acute effects of ecstasy use have reported that a similar trajectory for side effects, with subacute effects most apparent three to four days later and no longer apparent seven days later (Hoshi et al. 2004; Huxster et al. 2006).
Many studies in nonhuman animals suggest that frequent or high doses of MDMA can damage serotonin neurons, and some studies in ecstasy using humans suggest that repeated use, especially when heavy, can affect serotonergic function and specific domains of cognitive function. Ecstasy users exhibit impairment in specific areas of cognitive function, particularly verbal memory. However, when apparent, most long-term effects seem to be more strongly associated with heavy and not moderate use. The risk of impaired serotonin function or verbal memory after exposure to one to there doses of MDMA in the course of a controlled study remains possible, but evidence from retrospective and prospective studies of ecstasy users suggest that this risk is minimal after a low number of exposures. While there may also be risks related to psychological well-being such as increased symptoms of anxiety or depression, support for these longterm effects are even less strong than for the previously listed changes.

**Abuse Potential**

The US Drug Enforcement Administration (DEA) placed MDMA in Schedule 1, the most restrictive schedule reserved for compounds with high abuse potential and no medical value, and most other nations followed the lead of the US in making MDMA a tightly controlled substance. Studies in humans and nonhuman animals suggest MDMA possesses some abuse potential. However, it also appears that MDMA has fewer or less intensely rewarding effects than psychostimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA possesses moderate abuse liability that is greater than abuse liability for serotonergic hallucinogens but lesser than for psychostimulants. Mice, rats and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006), indicating that MDMA has rewarding properties in nonhuman animals. Monkeys chose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans (Fantegrossi et al. 2004), but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine (Lile et al. 2005; Wang and Woolverton 2007). Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence (von Sydow et al. 2002), though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence (Cottler et al. 2001), and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency (Topp et al. 1999).

**Reproductive and Developmental Toxicity**

Previous research supported a possible link between ecstasy use and birth defects.
(McElhatton et al. 1999), while an epidemiological study conducted in 2004 in a large cohort of pregnant women in England failed to support this link, at least in respect to a specific cardiac defect (Bateman et al. 2004). However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using ecstasy when they learn they are pregnant (Ho et al. 2001).

Several teams of researchers have performed studies of developmental toxicity in rodents (see for example (Koprich et al. 2003a; Koprich et al. 2003b; Piper and Meyer 2004; Williams et al. 2005). In some studies, the researchers administered large, repeated doses to pregnant rats, and in others, the MDMA was administered to neonatal rats. The researchers did not report gross structural abnormalities in rats exposed to high doses of MDMA in utero. However, studies of MDMA in neonatal rats found changes in numbers of serotonin or dopamine cells and impaired learning or memory, particularly when MDMA was administered from the 11th to the 20th day after birth. If this period is similar to the third trimester of human gestation, then it is possible that MDMA in humans could have similar developmental effects. Some researchers found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA (Green et al. 2005), while others found that it attenuated this response (Piper et al. 2005). Given differences in rodent development and thermoregulation, it is not clear whether either or both findings can be generalized to humans. Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA. Some investigators have claimed that MDMA affects sub-adult rats differently than adults. Giving somewhat large doses of MDMA to sub-adult rats produced long-term reductions in anxiety and impaired object recognition (Piper et al. 2004). An initial dose of MDMA in young rats also produced less of an increase in BT and fewer signs of “serotonin syndrome” when given another dose of MDMA in adulthood (Piper et al. 2005). These nonhuman animal studies suggest that adolescents could be more vulnerable to some effects of MDMA.

**Research trial data**

Information is being gathered and prepared. Side effects reported in the first clinical trials are similar to those reported in controlled studies, though anxiety may be more prevalent, due in part to the condition under study and in part to the nature of the setting, as participants are encouraged to confront emotionally upsetting thoughts, memories and feelings. In this setting anxiety is not chiefly viewed as a side effect, but as an element of the underlying disorder and the therapeutic process.
REQUEST FOR ADDITIONAL INFORMATION

If you receive this fax in error, please advise the sender immediately.
Si vous recevez cette télécopie par erreur, veuillez en aviser immédiatement l'expéditeur.

TO/À
Name/Nom: Dr. Rick Doblin
Date: 16/01/09
Organization/Organisme: MAPS
Tel./Tél.: 617-484-8711
Fax/Télécopieur: 617-484-8427
No. of Pages, including this page/N° de pages, incluant cette page: 2

FROM/DE
Name/Nom: Beata Wiatrowska, M.D.
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Tel./Tél.: 613-941-2132
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TITLE
Division/Unit: Clinical Trials & Special Access Programme/ Programme des essais cliniques et accès spécial aux médicaments
Bureau: Bureau of Pharmaceutical Assessment / Bureau de l'évaluation des produits pharmaceutiques
Directorate: Therapeutic Products Directorate / Direction Des Produits Therapeutiques
Room: Finance Building/ Edifice Finance
Building: Tunney's Pasture/Pré Tunney
Location: 0202C1
Address Locator: Ottawa, Ontario K1A 1B6
City/Province: Ottawa, Ontario
Postal Code: K1A 1B6
Website/site Web: www.hc-sc.gc.ca/hpb-dgps/therapeut

In accordance with Division 5 of the Food and Drug Regulations, we request clarification of the points on the following page so that we can continue our evaluation of your Clinical Trial Application (CTA) or CTA Amendment for:

Product: MDMA
Protocol Number: M-P4
Control Number: 126833
File Number: 9427-M2544-21C
Received in the Bureau on: 24/12/08

Please provide a complete response within 2 working days from the date of this request via facsimile to the sender. If the requested information is not received within 2 working days, a Not Satisfactory Notice may be issued.
Comment:

1. Please provide an updated information on studies of MDMA-assisted psychotherapy for PTSD and/or for potentially life threatening illness, if available.

2. Please provide more detailed reasons for the Swiss Government revoking permission to conduct MDMA assisted psychotherapy.

3. 
   a) What is the abuse/addiction potential of MDMA?
   b) What would be the estimated risk of abuse of MDMA for a participant in this trial after the completion of all MDMA assisted psychotherapy sessions?
   c) How does the abuse potential of MDMA compare to abuse potential of psychostimulants used as medications (e.g. methylphenidate, dexedrine etc.)?

4. Re: Inclusion criterion #2a: Please change the criterion 2a so that in addition to an unsuccessful course of appropriate psychotherapy a participant must have had at least one unsuccessful attempt at treatment with SSRI or mirtazapine or MAOI, and that treatment must have constituted an adequate trial (lasting for at least 3 months at optimal doses or the patient could not tolerate the treatment, i.e. the patients who simply refused a trial of any of the approved form of pharmacotherapy would not be eligible for this study).

5. Re: Inclusion criterion #2b: Please clarify that being a veteran with PTSD symptoms that have persisted for no less than 1 year but no more than 5 years would only qualify to participate in the study if this veteran also meets criterion #2a.

6. Re: Exclusion criterion #10: Please extend the time that the participant must be in remission for substance abuse or dependence (except caffeine and nicotine) to 12 months- i.e. full sustained remission, if substance abuse or dependence was an issue.

7. Re: Informed Consent:
   a) Re: risks of MDMA: Please provide the percentage of people expected to experience each of the listed potential adverse effects.
   b) Please clarify that people who had recently (in the last 365 rather than 60 days) problems with drug abuse should not take part in this study.
   c) Please provide what is the average expected increase in blood pressure and heart rate.

I would appreciate receiving your response in a paper (via fax), as well as an electronic (via e-mail) version.

Yours sincerely,

Beata Wiatrowska, M.D., FRCP(C)
If you do not receive all pages, please call the sender.

Si vous ne recevez pas toutes les pages, veuillez téléphoner à l'expéditeur
We have the following comments with respect to your CTA for MDMA 1.5 mg, 25 mg, 62.5 mg and 125 mg, Control 126833:

1. Please provide the narrative description of the drug substance synthesis that includes all reagents and solvents used in each step of the manufacturing process.

2. The following comments concern the specifications and batch analysis of the drug substance.
   a. You are requested to revise the specifications to include tests and limits for residue on ignition and heavy metals, and report the results for the batch to be used in this clinical trial.
   b. It is understood that the drug substance batch # MDM-94-HC will be used in this Canadian clinical trial. Please confirm. If you intend to use a different batch, the batch analysis of the new batch should be provided.

3. Please revise Section S6 to include the description of the drug substance container closure system.

4. Please report the quality standard for lactose (e.g. USP/NF) in Section P.4.

5. The following comments concern the specifications and batch analysis of the drug product.
   a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.
   b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis.

6. Please provide the description of the container closure system, and proposed storage conditions and shelf life of the drug product.

7. Please provide a commitment that the stability (appearance, assay, related substances/degradation products and dissolution) of the drug product will be monitored throughout the duration of the clinical trial.

8. You are requested to provide the certificate of suitability issued to the manufacturers of gelatin to be used in this clinical trial.

Rajkumar Kumarathasan, PhD.
Chemistry Advisor
Clinical Trials Quality Division
Office of Clinical Trials

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# Health Products and Food Branch

## Direction générale des produits de santé et des aliments

### QUALITY EVALUATION SUMMARY – CTAs (QES-CTA)

#### E.1 SUBMISSION SUMMARY

| Proprietary (Brand) Name of Drug Product | MDMA |
| Non-proprietary or Common Name of Drug Product | MDMA |
| Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient) | MDMA; 3,4 methylenedioxymethamphetamine |
| Company (Manufacturer/Sponsor) Name | Multidisciplinary Association for Psychedelic Studies |
| Dosage Form(s) | Capsule |
| Strength(s) | 12.5 mg; 20 mg; 62.5 mg; and 125 mg; |
| Route of Administration | Oral |
| Contact Information | Rick Doblin  
Phone: 617-484-8711; Fax: 617-484-8427 |

#### Type of Submission (and Phase for CTAs)

- **Proprietary (Brand) Name of Drug Product**: MDMA  
- **Non-proprietary or Common Name of Drug Product**: MDMA  
- **Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)**: MDMA; 3,4 methylenedioxymethamphetamine  
- **Company (Manufacturer/Sponsor) Name**: Multidisciplinary Association for Psychedelic Studies  
- **Dosage Form(s)**: Capsule  
- **Strength(s)**: 12.5 mg; 20 mg; 62.5 mg; and 125 mg;  
- **Route of Administration**: Oral  
- **Contact Information**: Rick Doblin  
  Phone: 617-484-8711; Fax: 617-484-8427

#### TPD Target Date

- 2009-01-23

#### Control Number / File Number

- 126833  
- 9427-M2544 - 21C

#### Number of Volumes

- C/T one folder Bin 2 dated 2008-12-24

#### Lead Clinical Bureau/Division

- Office of clinical trials

## Recommendation

This submission IS NOT recommended for clearance with respect to the Quality (Chemistry and Manufacturing) information.

| 1st Reviewer(s) | Udai Gill |
| Review Hours | 10 hrs + 2 |
| Start Date | 2009-01-07 |
| Completion Date | 2009-01-19 |

| Signatures | 1st Reviewer(s) |
| 2nd Reviewer(s) | |

| Report Access | 1:DPQ\Submission\CTA\HIJKLM\Multidisciplinary associates for psychedelic studies\MDMA\126833 cta-2009-r01.doc |
| References |  |

| Attachments |  |
Evaluator's Introduction/Discussion:

This is a review of a phase II CTA for a protocol No. MP-4: A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

Dose Formulation: Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg.

Dosing: An Experimental dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later.

Placebo: Active Placebo (low dose MDMA + Lactose); active placebo doses are 12.5 mg and 25mg. Active placebo doses of MDMA will also contain the inactive substance, lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

Drug Substance:
The drug substance, MDMA [(+/-)3,4 - methylenedioxymethamphetamine, HCl] is sourced from Lipomed AG, Switzerland. MDMA batch No. MDM-94-HC/94.1B5.5. The sponsor will be asked to provide a current C of A for the drug substance including results for impurities. The sponsor will be asked to revise the container closure system information in S6. The information in stability testing section is not complete and stability testing data is not provided.

Drug Product:
The drug product is compounded at Kripps Health Care RX pharmacy, Vancouver BC. Racemic MDMA is placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg. The active placebo capsules contain lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

The drug product is compounded at Kripps Health Care RX pharmacy, Vancouver BC.
PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION SPONSOR

We have the following comments with respect to your Phase II CTA for MDMA, strengths at 12.5 mg, 25mg, 62.5mg and 125mg per capsule, Control no. 126627:

1. Please provide the narrative description of the drug substance synthesis that includes all reagents and solvents used in each step of the manufacturing process.

2. The following comments concern the specifications and batch analysis of the drug substance.

   a. You are requested to revise the specifications to include tests and limits for residue on ignition and heavy metals, and report the results for the batch to be used in this clinical trial.

   b. It is understood that the drug substance batch # MDM-94-HC will be used in this Canadian clinical trial. Please confirm. If you intend to use a different batch, the batch analysis of the new batch should be provided.

3. Please revise Section S6 to include the description of the drug substance container closure system.

4. Please report the quality standard for lactose (eg. USP/NF) in Section P.4.

5. The following comments concern the specifications and batch analysis of the drug product.

   a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.

   b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis.

6. Please provide the description of the container closure system, and proposed storage conditions and shelf life of the drug product.

7. Please provide a commitment that the stability (appearance, assay, related substances/degradation products and dissolution) of the drug product will be monitored throughout the duration of the clinical trial.

8. You are requested to provide the certificate of suitability issued to the manufacturers of gelatin to be used in this clinical trial.
Modules 2 and 3: Common Technical Document Summaries and Quality

**Study Title:** A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada  
**Sponsor:** Multidisciplinary Association for Psychedelic Studies  
**Principal Investigator:** Dr. Ingrid Pacey MB.BS. FRCP[C]  
**Study Number:** M-P4

Quality Overall Summary and Referenced Documents
Primary Efficacy and Safety Objectives:
The primary objective of this study is to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with treatment-resistant Posttraumatic Stress Disorder (PTSD). Symptoms of PTSD will be assessed via Clinician-Administered PTSD Scale (CAPS). The Posttraumatic Diagnostic Scale (PDS) will be used as a secondary measure of PTSD symptoms. The investigators compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) session.

Trial Objectives

Primary Efficacy and Safety Objectives: The primary objective of this study is to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with treatment-resistant PTSD. Symptoms of PTSD will be assessed via Clinician-Administered PTSD Scale (CAPS). The Posttraumatic Diagnostic Scale (PDS) will be used as a secondary measure of PTSD symptoms. The investigators compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) session.
The investigators will also gather information on physiological effects and side effects after MDMA.

**Secondary Objectives:** The secondary objective of this study is to investigate the effects of MDMA-assisted psychotherapy on symptoms of depression in people with PTSD. Depression will be assessed via the Beck Depression Inventory (BDI). The investigators will compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

**Study Design and Duration**

The proposed pilot study will employ a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.

Participants in the active placebo condition will have the opportunity to enroll in an open-label study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD and depression symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling
The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental condition are identical to those in use in other MAPS-supported studies of Dosing Regimen.

Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg. MDMA will be obtained from Lipomed AG. Active placebo doses of MDMA will also contain the inactive substance lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

Drug Formulation

Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg. MDMA will be obtained from Lipomed AG. Active placebo doses of MDMA will also contain the inactive substance lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental condition are identical to those in use in other MAPS-supported studies of...