

**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**

**(To be submitted to Ethics Board Health Canada and, if approved, to FDA under IND#63,384)  
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### **Introductory Statement**

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). This study has been designed as part of an international, multi-site program of research sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS, [www.maps.org](http://www.maps.org)), a USA-based non-profit research and educational organization. MAPS' long-term goal is to develop MDMA into a prescription medication approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada. MAPS is currently the only organization in the world of which we are aware sponsoring research into the therapeutic potential of MDMA.

MAPS is currently sponsoring under FDA IND #63,384 a nearly completed pilot study of MDMA-assisted psychotherapy in 21 patients with treatment-resistant posttraumatic stress disorder (PTSD), taking place in Charleston, South Carolina under the direction of Dr. Michael Mithoefer. Twenty out of 21 subjects have already completed the protocol. The final experimental session for the 21<sup>st</sup> subject occurred on July 18, 2008 and the final two-month follow-up evaluation will take place around September 18, concluding the study. Preliminary results are remarkably promising with no drug-related Serious Adverse Events (SAEs) and statistically significant results supporting the efficacy of MDMA-assisted psychotherapy (Wagner 2008, personal communication). A separate longer-term follow-up of participants a year or more after study participation has been approved by our IRB and will be initiated soon.

MAPS is sponsoring two additional ongoing pilot studies of MDMA-assisted psychotherapy in patients with PTSD, one in Switzerland under the direction of Dr. Peter Oehen, and one in Israel, under the direction of Dr. Moshe Kotler, Chair, Department of Psychiatry, Tel Aviv University, Sackler School of Medicine, and former Chief Psychiatrist of the Israeli Defense Forces. Both of these studies are designed for twelve subjects and are scheduled to be completed before the end of 2009. All studies are using the same primary outcome variable, the Clinician Administered PTSD Scale (CAPS), enabling examination of results across all studies, and meta-analyses of data pooled across each pilot study. All of MAPS' studies conducted outside of the US have been approved by regulatory authorities in those countries and have been submitted to FDA and are also being conducted under FDA IND 63,384.

MAPS has also helped initiate and fund an FDA-approved study investigating MDMA-assisted psychotherapy in people with anxiety related to advanced-stage cancer. This study is taking place at Harvard Medical School's McLean Hospital, under the direction of Dr. John Halpern MD, the Sponsor/Investigator. The second of twelve subjects has been enrolled. The first subject has completed the study safely with reports of reduced anxiety and pain (Halpern 2008).

This proposed Canadian pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, eight of 12 people will receive a dose of MDMA expected to be fully therapeutic (experimental dose) and four of 12 will

receive threshold “active placebo” dose of MDMA during three sessions scheduled three to five weeks apart. PTSD symptoms will be assessed at baseline on entry to the study and six weeks after the third double-blind MDMA-assisted psychotherapy session. Cognitive function will also be assessed at baseline and again six weeks after the third experimental session. Study participants will also receive psychotherapy before and after each day-long experimental MDMA-assisted psychotherapy session.

Participants who received active placebo during the course of the randomized study segment have the opportunity to take part in a second study segment that follows nearly identical procedures, but with participants receiving experimental dose MDMA in an open-label context. If the investigators conclude after the end of the randomized or open-label study segment that a participant receiving experimental dose MDMA has responded only partially or not at all, and if the participant and investigators agree to it, the participant may take part in a fourth experimental-dose MDMA-assisted session, with PTSD symptoms and depression assessed six weeks afterwards.

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the psychedelic drug mescaline. It was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s (Freudenmann et al. 2006; Shulgin 1986). 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 (Greer and Tolbert 1986; Saunders 1993; Stolaroff 2004). Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.

Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD (Adamson 1985; d'Otalora 2004; Greer and Tolbert 1998; Metzner and Adamson 2001). 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” (Greer and Tolbert 1998). 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 (Greer and Tolbert 1998). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlender 1990). 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.

MDMA became illegal in the US and then internationally shortly after a rise in use of MDMA outside the confines of psychotherapy. Ecstasy (material represented as MDMA) continues to be used throughout the world. Serious adverse events such as hyperthermia, hyponatremia or liver damage have occurred in association with ecstasy use, though these are relatively rare given the widespread use of ecstasy. It is notable that the purity and potency of illicit ecstasy is often unknown. Recent surveys of ecstasy tablets indicate that up to 40% are adulterated or contain no MDMA (Baggott et al. 2000; Cole et al. 2002). There is evidence that the use of frequent, high doses of Ecstasy in uncontrolled settings exacerbates its risks. The majority of serious adverse events after Ecstasy consumption have occurred in conditions of high ambient temperature, long periods of strenuous activity (dancing) and insufficient or uncontrolled fluid intake. All of these environmental circumstances may enhance or exacerbate problematic effects of Ecstasy. By contrast, people taking part in MDMA-assisted psychotherapy do not experience these behavioral or environmental factors.

Initial Phase 1 human trials of MDMA in approximately 390 subjects have demonstrated that the drug can be administered safely under controlled conditions. No drug-related Serious Adverse Events (SAEs) have been reported during the course of the ongoing MDMA/PTSD Phase II studies in the US, Switzerland and Israel. Preliminary examination of neuropsychological data from the US study has found no deterioration in condition after MDMA-assisted psychotherapy.

If data from MAPS' pilot studies continue to produce promising results, then MAPS will use the information gathered from these studies to formulate two large (N = approximately 280) multi-site Phase III studies of MDMA-assisted psychotherapy, one to be conducted throughout the United States and Canada and one to be conducted throughout Europe and Israel. MAPS' Clinical Plan (Doblin 2002) estimates that this process will require at least five years and will involve at least 560 subjects.

## **Background**

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder arising after a personally threatening life-event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. The DSM IV (APA 1994) criteria for PTSD include:

- A. Exposure to a significant traumatic event accompanied by an intense acute emotional response.
- B. Persistent re-experiencing of the event or aspects of the experience.
- C. Persistent avoidance of stimuli associated with the event, and/or withdrawal from some aspects of life.
- D. Persistent symptoms of increased arousal.
- E. The above symptoms must last for more than one month for Acute PTSD and more than three months for Chronic PTSD.

PTSD affects an estimated 8% of the general population at some point during their lifetime (Kessler et al. 1995), as reported in a national survey of mental disorders in the general population of the US. There are still questions concerning what are the best treatments for this debilitating psychiatric disorder (Montgomery and Bech 2000). People with PTSD face challenges in relationships and with work productivity (Brady et al. 2000). An array of psychotherapeutic options exists for treating PTSD, and two SSRIs (Zoloft and Paxil) are approved as PTSD treatments in the US. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies (Foa et al. 1999; Resick and Schnicke 1992), and at least one study of Paxil indicated that men with PTSD did not respond to this drug (Brady et al. 2000). These findings suggest that there is still substantial need for innovative treatments for PTSD.

Although presently we are not aware of any national surveys of lifetime PTSD prevalence in Canada, it is likely that the percentage of Canadians experiencing PTSD is similar to the 8% to 11% listed in samples from the United States and Europe. Likewise, a large prospective, longitudinal epidemiological study of adolescents and young adults in Germany showed a lifetime prevalence of PTSD, including subthreshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased to 10.3%. (Perkonigg et al. 2000). A survey of 3062 women in Ontario reported a 10.7% lifetime prevalence rate (Frise et al. 2002). A study of Canadian peacekeepers reported higher rates of prevalence, with peacekeepers with single deployment diagnosed with PTSD at a rate of 10.9% and a 14.8% rate in peacekeepers who were deployed more than once (Richardson et al. 2007). These findings suggest that Canadians have PTSD at rates comparable to the US and Europe and that as expected, certain populations will experience higher rates of PTSD.

PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. Acting Inspector General Jon A. Wooditch testified to the US Congressional Committee On Veterans' Affairs Subcommittee On Disability Assistance And Memorial Affairs that in 2004, the US Veterans Administration spent over \$4.3 billion on disability payments to over 215,000 veterans with PTSD (2005). The search for novel and more effective treatments is therefore of major public health and economic significance. In the US National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third of the patients still had symptoms several times per week after 10 years (Kessler et al. 1995). Generally, the number of people who do not improve after treatment can be high, between 40% and 60%. In a 2002 comparison of two types of psychotherapy for women with PTSD after sexual assault, 47% of each treatment group still were diagnosed with PTSD with high enough CAPS scores (Resick et al. 2002) and another study reported similar figures (Foa et al. 1999).

### **PTSD and MDMA-assisted psychotherapy**

To date the treatment of PTSD has primarily been a psychotherapeutic treatment, 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 EMDR also proved to be effective in treating some aspects of PTSD symptoms (Ursano et al. 2004). Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms (Hamner et al. 2004). However, a recent meta-analysis concluded that all “bona fide” psychotherapies, including all those listed above, are similarly effective with PTSD (Benish et al. 2008).

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy. MDMA possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients (Greer and Tolbert 1998; Metzner and Adamson 2001; Stolaroff 2004; Widmer 1998). Treatment consists of several administrations of MDMA-assisted psychotherapy within the context of a brief to moderate course of non-drug psychotherapy. MDMA-assisted psychotherapy is hypothesized to reduce or ameliorate the hypervigilance and emotional numbing and withdrawal experienced by individuals diagnosed with PTSD.

Anecdotal accounts, an uncontrolled clinical trial, and data from an ongoing controlled trial described above all suggest that MDMA may provide unique benefits to people with PTSD when administered in combination with psychotherapy. It may assist people in confronting memories, thoughts and feelings related to the trauma without increasing fear in response to this confrontation. An increase in self-acceptance and increased feelings of closeness to others may also assist people with PTSD as they work with psychotherapists.

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. One approach is to discover drugs that directly counteract these neurobiological changes. Paxil and Zoloft are the only two drugs approved by the FDA in the US for treating PTSD, and are known to affect the serotonergic components of PTSD. They may also block the down-regulation of brain-derived neurotrophic factor, but it is not known whether it can arrest and reverse the hippocampal atrophy found in PTSD (Nibuya et al. 1996). Another approach to treatment of PTSD is to develop drugs and/or psychotherapeutic treatments that will indirectly interrupt the destructive neurobiological changes by decreasing or eliminating the stress reactions to triggers and the chronic hyperarousal of PTSD. Reports of past experience with MDMA-assisted psychotherapy suggest that it may also counteract the effects of PTSD. In fact, the biologic and psychotherapeutic approaches overlap and re-enforce each other. Knowledge about the connections between the neurobiological and the therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala (Gamma et al. 2000). This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD (Davis and Shi 1999; Rasmusson and Charney 1997).



To date, Phase I trials have been conducted by eight research teams in the United States, England, Spain, Switzerland, and the Netherlands, with MDMA administered to approximately 390 subjects overall without the occurrence of any serious adverse events (see for example Cami et al. 2000b; Chang et al. 2000; Dumont and Verkes 2006, review; Kolbrich et al. 2008; Kuypers et al. 2008; Tancer and Johanson 2003; Vollenweider et al. 1998). When MDMA is used in doses similar to those proposed for this study, and in a controlled setting, the risk/benefit ratio is favorable. By and large, MDMA appears to have risks that are similar to those of other structurally-related sympathomimetic compounds (Mas et al. 1999; Tancer and Johanson 2003), such as amphetamine (Adderall), that have been used clinically for many years.

Acute effects reported in controlled studies are in agreement with those reported in earlier uncontrolled studies (Downing 1986; Greer and Tolbert 1986) and anecdotal reports (Adamson 1985; Widmer 1998). These include stimulant-like effects and hallucinogen-like effects. Though to date, no controlled study has confirmed acute changes in feelings of closeness to others or empathy, this effect may be reflected in increased sociability or friendliness (Tancer et al. 2003) and has been informally noted in at least one publication (Vollenweider et al. 1998).

There has been no evidence of significant or lasting toxicity in subjects participating in Phase I studies of MDMA. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e. g. Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Reneman et al. 2001; Thomasius et al. 2003). In contrast, all available Phase I 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. As described in more detail below, more 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. Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to serve as 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.

### **Previous Clinical Experience with MDMA**

Prior to its scheduling and international regulation, MDMA was used in psychotherapy to treat neuroses, relationship difficulties, and PTSD (Adamson 1985; d'Otalora 2004; Gasser 1994; Greer and Tolbert 1986; Greer and Tolbert 1998; Stolaroff 2004; Widmer 1998). Anecdotal and narrative accounts of MDMA-assisted psychotherapy reported successful treatment of PTSD. People reported reduced PTSD symptoms and improved

quality of life. It should be noted that during this period in time, MDMA may have been given to thousands of individuals without any fatalities or serious adverse events (Holland 2001; Rosenbaum and Doblin 1991). Greer and Tolbert's (1986) uncontrolled, non-blinded study of MDMA in a therapeutic context found that most of the 29 individuals with mild to moderate psychological difficulties reported obtaining some lasting benefits after MDMA-assisted therapy (Greer and Tolbert 1986).

As described in the Introductory Statement, a sponsor-supported pilot study of MDMA-assisted psychotherapy in 21 people with PTSD is almost completed in Charleston, South Carolina. This study employs the CAPS as a 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 (see attached report).

The ongoing study in Switzerland comparing the effects of 125 mg MDMA followed by a supplemental dose of 62.5 mg with 25 mg MDMA and a supplemental dose of 12.5 mg in people with PTSD has enrolled six of 12 subjects. The design of the study permits the investigator to provide up to two additional open-label sessions to individuals who do not respond to three experimental dose MDMA-assisted psychotherapy sessions. In these additional sessions, the investigator is permitted to administer either 125 mg followed by a supplemental dose of 62.5 mg or a higher dose of 150 mg followed by 75 mg supplemental dose. To date, one participant has received two additional experimental sessions with 150 mg MDMA and supplemental dose without incident. This study is estimated to conclude before the end of 2009.

The ongoing study in Israel comparing the effects of 125 mg MDMA followed by a supplemental dose of 62.5 mg with 25 mg MDMA followed by a supplemental dose of 12.5 mg in people with PTSD is currently designed to have two experimental sessions. One subject out of 12 has completed the study. This study is estimated to conclude before the end of 2009.

The potentially therapeutic effects of MDMA were initially investigated starting in 2000 in a MAPS-sponsored dose-response pilot study in Spain in women survivors of sexual assault with treatment-resistant PTSD. Unfortunately, the study in Spain was halted in 2002 due to political pressure from the Madrid Anti-Drug Authority. Prior to its suspension, six women were enrolled in this study without any adverse events or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 to 75 mg. MAPS is currently exploring the possibility of starting a new pilot study in Barcelona, Spain, under the direction of the PI from our initial study.

## Summary

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 two MDMA-assisted sessions with 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 scheduled three to five weeks apart, during which they will randomly receive either the experimental or active placebo dose of MDMA. Participants will undergo one non-drug-psychotherapy session 24 h after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. PTSD symptoms 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.

Baseline assessments of symptoms of PTSD and depression conducted by an independent rater will be compared with assessments made six weeks after the third double-blind (experimental) session. Baseline assessment of neurocognitive function will be compared with assessments made six weeks after the third double-blind (experimental) session. 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 symptoms and depression six weeks after the third open-label session. Participants may undergo a fourth and open-label session of MDMA-assisted psychotherapy after the evaluation at the end of stage 1 or stage 2 if the investigators conclude that the participant responded only partially or not at all to the treatment and the participant agrees to undergo the additional session. The participant and investigators may decide to administer doses of 150 followed 2.5 hours later by a supplemental dose of 75 mg MDMA during this fourth contingent open-label session. The independent rater will assess PTSD symptoms six weeks after the fourth optional open-label session.

## Principal Investigator

Ingrid Pacey MBBS FRCP[C] 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 has also written papers on Holotropic Breathwork and has taught others the technique. She worked as a clinical supervisor in the UBC Student Women's Office from 1992 to 1996.

## Co-Investigators

Andrew Feldmár, 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. See his work in Hungary as presented on the website of the Feldmár Institute: <http://www.feldmarinstitute.hu/>. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. The independent rater will be Karen Tallman Ph.D, a clinical psychologist who has worked as a clinical psychologist for 15 years and has conducted psychiatric diagnostic and competency assessments. She has a private practice and has worked at the Short Term Assessment and Treatment Centre at Vancouver General Hospital.

## Ethics

The trial will not be initiated until appropriate Health Canada and Institutional Review Board (IRB) approval of the protocol and the informed consent document has been obtained. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. The protocol will also be submitted to FDA under MAPS' IND 63,384.

This trial will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, and applicable standard operating procedures (SOPs). The trial will be conducted under a protocol reviewed and approved by an IRB; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

## Informed Consent of Subject

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

The information about the trial must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject's legal rights, the information should include that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the trial and to consider participation. The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

The principal investigator or the co-investigator therapist will provide a copy of the signed informed consent to the subject, and will maintain the original in the investigator's study file.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive approval from an ethics board before use.

The subject should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g. pathologist report), it will be obscured before the copy of the document is supplied to the sponsor.

Written consent to take part in this study includes giving the investigators permission to view the participant's recent medical records to assess study eligibility. Information necessary for study participation includes physical examination, tests of metabolic and liver function, thyroid panel and psychiatric diagnostic interview.

### **Recruitment and Screening**

Candidates for study participation will be recruited by letters of referral sent to psychiatrists and psychotherapists and through word of mouth. One of the investigators will interview prospective participants by telephone to learn if they meet basic eligibility criteria. If the prospective participant is interested in taking part in the study, the investigators will provide the prospective participant with consent materials through postal mail or situated on a website, for review and consideration. If, after review, an applicant remains interested in taking part in the study, then he or she will meet with the investigators to complete the consent process. Applicants will complete a quiz addressing questions relating to information contained in the consent forms, with the investigators going over quiz responses with the prospective participant to ensure that he or she correctly understands study procedures, risks and benefits.

### **Study Objectives**

The study seeks to examine whether a fully active (experimental) versus active placebo dose of MDMA-assisted psychotherapy will reduce or attenuate PTSD symptoms and whether there is sufficient safety for this innovative treatment.

*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 will analyze changes in PTSD symptoms during the start of the study, six weeks after the third experimental session, and six weeks after the optional fourth session for partial or non-responders. Scores on the PDS will also be compared at the start of the study, six weeks after the third experimental session and six weeks after the optional fourth session for partial or non-responders.

The investigators will administer the CAPS to participants who received active placebo and opted to enroll in the open-label study segment six weeks after their final experimental open-label session. They will compare CAPS scores six weeks after the third experimental session and six weeks after the third open-label session, and they will also compare scores at the start of the randomized session with scores six weeks after the third open-label 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 examine changes in BDI scores at baseline, six weeks after the third experimental session, and six weeks after the optional fourth session for partial or non-responders .

The investigators will administer the BDI to participants who received active placebo and enrolled in the open-label study segment, comparing scores at the start of the open-label segment and scores six weeks after the third open-label session. They will compare depression symptoms six weeks after the third experimental session and six weeks after the third open-label session, and they will also compare study baseline scores and scores six weeks after the third open-label session.

The investigators will also compare scores at the open-label study segment baseline with scores six weeks after a participant's final open-label session.

## **General Investigational Plan**

### **Study Population and Characteristics**

The study will enroll twelve (12) participants aged 18 years or older. The study will enroll both men and women. Eight of 12 participants will be randomly assigned to receive the experimental dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg 1.5 to 2.5 hrs later and four will be randomly assigned to receive the active placebo dose of 25 mg followed by a supplemental dose of 12.5 mg 1.5 to 2.5 hrs later. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

### *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) (Foa et al. 2003; Jaycox et al. 2002; Krupnik 2002; Resick and Schenk 1992). 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 (Brady et al. 1994; Faustman and White 1989).
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 non-steroidal 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 Dr. Pacey's clinic 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 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, 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.
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 60 days.
11. Any person who is not able to give adequate informed consent.

### **Planned Duration of Study**

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. Participants who undergo the optional fourth session and attendant integrative therapy will be enrolled for approximately four more weeks, with the final follow-up assessments six weeks afterwards, so that in this case the study could last about six and a half months.

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 two months after the final open-label MDMA-assisted therapy session, for a total of about 8 months. Participants who undergo the optional fourth session and attendant integrative therapy will be enrolled for approximately four more weeks, with the final follow-up assessments six weeks afterwards, so that in this case the study could last about six and a half months, for a total of about ten and a half months.

### **Drug Description and Dosage**

Upon enrollment in the study, the participant will be randomly assigned to the active placebo or experimental dose condition. The two therapist-investigators and the independent assessor will remain blind to condition assignment. If there is an adverse

event or other emergency requiring knowledge of the participant's condition assignment, the blind may be broken for an individual participant.

Participants in the active placebo condition will be assigned to receive three experimental sessions with an initial dose of 25 mg MDMA followed 1.5 to 2.5 hours later by a supplemental dose of 12.5 mg MDMA. Participants assigned to the experimental dose condition will receive three experimental sessions with an initial dose of 125 mg followed 1.5 to 2.5 hours later by a supplemental dose of 62.5 mg MDMA. Eight of 12 subjects, or 66.6%, will be assigned to the experimental dose condition, and four of 12, or 33.3%, will be assigned to the active placebo condition.

Participants in the experimental dose condition that the investigators evaluate as partial responders or non-responders may, with the agreement of participants and investigators, receive an optional fourth session, either with doses of 125 mg followed by 62.5 mg or a somewhat higher dose of 150 followed by 75 mg MDMA. The investigators may employ the fourth session and the higher dose if in their clinical judgment it may benefit the participant without causing harm.

Participants in the active placebo condition will be offered the option of undergoing a study segment using nearly identical procedures to those in the randomized study segment but with participants receiving experimental dose MDMA within an open-label context.

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 the studies of MDMA-assisted psychotherapy currently underway in the US, Switzerland and Israel. Previous researchers have also used doses within this range (Cami et al. 2000a; Freedman et al. 2005; Grob et al. 1996; Harris et al. 2002; Kuypers et al. 2006; Liechti et al. 2001). Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA (Cami et al. 2000b; de la Torre et al. 2000a; Freedman et al. 2005; Grob 2001; Mas et al. 1999; Tancer and Johanson 2003). Prior to the time MDMA was placed in schedule 1 identical or similar doses and regimens were used in psychotherapy (Greer and Tolbert 1986; Metzner and Adamson 2001; Stolaroff 2004). The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective drug 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 (Grob 2001; Harris et al. 2002) and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is not expected to produce a significant reduction in anxiety or a significant increase in access to emotionally upsetting material, though this dose may produce slight alterations in consciousness, such as increased relaxation or tension (Harris et al. 2002).

During the fourth MDMA-assisted psychotherapy session for people who appear to be partial responders or nonresponders, participants may receive doses of 150 and 75 mg MDMA if the investigators and participant are in mutual agreement as to using this dose. The dose of 150 mg MDMA used in previous research. The dose is within the range of doses of MDMA used in therapeutic settings in the past, in some controlled studies of MDMA, and in our Swiss MDMA/PTSD study (de la Torre et al. 2000a; Freedman et al. 2005; Greer and Tolbert 1986; Kolbrich et al. 2008). Recent findings of inter-subject variation in MDMA metabolism suggest that some participants may benefit from this higher dose while others may not need it or might even experience intensified side effects (Kolbrich et al. 2008). The investigators wish to examine if participants who are less sensitive to the therapeutic effects of a fully active dose of MDMA will be more responsive to a higher dose. The investigators in this study will use their discretion and clinical judgment to determine if and when they will employ the higher dose during the optional fourth session.

**Table 1**

Drug Doses for proposed study

	<b>Initial Dose</b>	<b>Supplemental Dose</b>	<b>Cumulative Dose</b>
<i>Active Placebo</i>	25 mg	12.5 mg	37.5 mg
<i>Experimental Dose</i>	125 mg	62.5 mg	187.5 mg
<i>Open-Label Optional Larger Dose (4<sup>th</sup> Session Only)</i>	150 mg	75 mg	225 mg

**Method**

The researchers will employ a randomized, double-blind, active-placebo controlled design to compare symptoms of PTSD and depression before and after receiving MDMA-assisted psychotherapy with an experimental or active placebo dose of MDMA. The double-blind 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. An independent rater not involved with performing psychotherapy will assess symptoms of PTSD with CAPS and PDS, and depression with the BDI at study baseline and six weeks after the third experimental session.

The investigators will break the blind individually for each participant after the assessments six weeks after the third experimental session. Experimental dose condition participants that the investigators determine to be partial or non-responders may undergo a fourth optional open-label session. Study participants and researchers must mutually agree to extend the study to include a fourth open-label session. The CAPS will be re-administered six weeks after this fourth session.

Participants who learn they are assigned to active placebo can enroll in the open-label study segment. Active placebo condition participants enrolled in Stage 2 will have three sessions with experimental-dose MDMA. Participants in stage 2 may undergo a fourth

optional open-label session if they appear to be partial responders or nonresponders after open-label MDMA-assisted psychotherapy. As is the case for experimental dose participants, there will be mutual agreement concerning the occurrence of this fourth MDMA-assisted session. The independent rater will assess all participants in the open-label segment t six weeks after their third open-label session. Should a fourth session be conducted, the CAPS would be readministered six weeks after this fourth session.

**Time and Events for Randomized Study segment**

Table 1: Schedule of Events for Randomized study Segment																					
Time and Events M-P4	Baseline and Screening				Therapy and Evaluation 1					Therapy and Evaluation 2					Therapy and Evaluation 3						
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	
Visit #	Prestudy	Consent	Screening/Baseline	Intro Psychotherapy	Intro psychotherapy2	Intro psychotherapy3	Experimental 1	Integrative Therapy1	Integrative Therapy2	Integrative Therapy3	Experimental 2	Integrative Therapy4	Integrative Therapy5	Integrative Therapy6	Experimental 3	Integrative Therapy 5	Integrative Therapy6	Integrative Therapy7	6 wk post V11	End Randomized Segment	
Approximate Study Day					14	21	28	28	35	42	49	56	63	70	77	84	91	98	112	112	
Visit Timing and Windows		Post telephone	[Post-consent, may be same day]	(-4/+3 d)	Post V4	Post V5	post V6	24 h post-experiment session 1	Between V6 and V11	Post-V9	>3-5 wks post V6	24 h post V11	Post V11	Post V13	>3-5 w post V11*	24 h post V15	Post V15	Post V17	6 wk post V15	May be same day as V19	
Study Staff	Ingrid+Andrew	Ingrid+Andrew	Physician, Ingrid+Andrew, IA	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew, IA	Ingrid+Andrew	
Telephone Screening	X																				
Provide consent materials		X																			
Study informed consent		X																			
Medical Examination			X																		
ECG			X																		
Liver FCT			X																		
Drug Screen			X				X				X				X						
Pregnancy Screen			X				X				X				X						
Psychiatric examination			X																		
SCID			X																		
Baseline evaluation			X																		
CAPS			X																	X	
PDS			X																	X	
BDI			X																	X	
RBANS			X																	X	
PASAT			X																	X	
Study Enrollment			X																		
Record to audio & video				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Psychotherapy-No Drug				X	X	X		X	X	X		X	X	X		X	X	X			
General Well-Being				X	X	X		X	X	X		X				X				X	
Administer MDMA							X				X				X						
Psychotherapy + MDMA							X				X				X						
Administer higher dose MDMA																					
Blood Pressure							X			X	X				X						
Pulse							X			X	X				X						
Body Temperature							X			X	X				X						
SUD							X			X	X				X						
Common Side Effects							X	X		X	X				X						
Overnight stay							X			X	X				X						
Serious Adverse Events			X	X	X	x	X	X	X	X	X	X			X	X				X	
Adverse Events Requiring Dr Visit			X	X	X	x	X	X	X	X	X	X			X	X				X	
Unblinding																					X
Consent for Stage 2/open-label																					X
RRPQ																					x
End Randomized phase																					x
IA=Independent Assessor																					
-Optional & for nonresponders only																					

**Time and Events for Open-Label Study Segment after Randomized Study for Active Placebo Participants**

Time and Events for Stage 2	Baseline and Screening				Therapy and Evaluation 2						Therapy and Evaluation 3						Optional Open-Label 4 (Post Stage 1 / Stage 2)							
Visit #	V20	V21	V22	V23	V24	V25	V26	V28	V29	V30	V31	V32	V33	V34	V35	V36	V37	V38	V39	V40	V41	V42	V43	
Type of Visit	Consent	"Baseline"	Review/Intro Therapy	Open-Label 1	Integrative Therapy6	Integrative Therapy9	Integrative Therapy10	Open-Label 2	Integrative Therapy11	Integrative Therapy12	Integrative Therapy13	Open Label 3	Integrative Therapy14	Integrative Therapy15	Integrative Therapy16	6 wk post Open-Label 3	End Stage 2	Review & re-intro-session 2 <sup>a</sup>	Optional Open-Label 4 <sup>a</sup>	Integrative Therapy17 <sup>a</sup>	Integrative Therapy18 <sup>a</sup>	Integrative Therapy19 <sup>a</sup>	Six wks post V38 <sup>a</sup>	
Approximate Study Day	112	113	120	127	128	135	142	149	150	157	164	171	172	179	186	213		220	227	228	236	343	244/258	
Visit Timing and Windows	On/Post V15	On/Post V19	Post V16	Post V17	24 h post Open Label 1	Between V24 and V28	Post V25	*=>3<5 wks post V23*	24 h post Open Label 2	Between V29 and V32	Post V30	*=>3<5 wks post V28*	24 hours post Open Label 3	Between V33 and V36	Post V34	6 wk post V32		Post V36	*=>3<5 wks post V28*	24 h post V31	Between V32 and V34	Post V33	2 mo Post V27/V31 <sup>a</sup>	
Study Staff	Ingrid/Andrew	Karen, Andrew/Ingrid	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew, Karen	Ingrid/Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid/Andrew, Karen
Telephone Screening																								
Provide consent materials	X																							
Study informed consent	X																							
Medical Examination																								
Liver FCT																								
Drug Screen		X		X				X				X								X				
Pregnancy Screen		X		X				X				X								X				
Psychiatric examination		X																						
SCID																								
Baseline evaluation		X																						
CAPS		X														X							X	
PDS		X														X							X	
BDI		X														X							X	
RBANS		X																						
PASAT		X																						
Study segment enrollment	X																							
Psychotherapy-No Drug			X		X	X	X		X	X	X		X	X	X			X		X	X	X		
General Well-Being			X		X	X	X		X	X	X		X	X	X	X	x	X		X	X	X	X	
Administer MDMA				X				X				X								X				
Psychotherapy + MDMA				X				X				X								X				
Administer higher dose MDMA												X*								X*				
Blood Pressure				X				X				X								X				
Pulse				X				X				X								X				
Body Temperature				X*				X*				X*								X*				
SUD				X				X				X								X				
Common Side Effects				X	X			X	X			X	X							X	X			
Overnight stay				X				X				X								X				
Serious Adverse Events		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X			X	
Adverse Events Requiring Dr Visit				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	
RRPQ																	X						X	
End Stage 2																							X	
*=if appropriate																								

**Additional Open-Label Session for Non-Responders (after Randomized Study Segment or Stage 2)**

Schedule of Events for Optional Open-Label Session for Nonresponders (Post Stage 1 or Stage 2)						
<i>Time and Events M-P4</i>	Optional Open-Label					
Visit #	v38	V39	V40	V41	V42	V43
Type of Visit	Review/Intro Therapy <sup>^</sup>	Open-Label Optional <sup>^</sup>	Integrative Therapy <sup>8^</sup>	Integrative Therapy <sup>9^</sup>	Integrative Therapy <sup>10^</sup>	6 wk post V23 <sup>^</sup>
Approximate Study Day	120	127	128	135	142	200/222
Visit Timing and Windows	Post V19	Post v22	24 h post Open Label 1	Post V22	Post V25	6 wk post V23
Study Staff	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid/Andrew, Karen
Telephone Screening						
Provide consent materials						
Drug Screen		X				
Pregnancy Screen		X				
Psychiatric examination						
Baseline evaluation						
CAPS						X
PDS						X
BDI						X
RBANS						
PASAT						
Study Enrollment						
Record to audio & video	X	X	X	X	X	
Psychotherapy-No Drug	X		X	X	X	
General Well-Being	X		X	X	X	
Administer MDMA		X				
Psychotherapy + MDMA		X				
Administer higher dose MDMA		X*				
Blood Pressure		X				
Pulse		X				
Body Temperature		X*				
SUD		X				
Common Side Effects		X	X			
Overnight stay		X				
Serious Adverse Events	X	X	X	X	X	X
Adverse Events Requiring Dr Visit	X	X	X	X	X	X
RRPQ						X
End Study segment						X
IA=Independent Assessor						

## Assessments and Measures

Screening and outcome measures were chosen to be well-recognized in the literature and because of prior use in other sponsor-supported studies of MDMA-assisted psychotherapy in people with PTSD.

Psychiatric diagnoses will be made through the Structured Clinical Interview for Diagnoses (SCID), and PTSD symptoms will be measured by the Clinician Administered PTSD Scale (CAPS) during screening to determine whether an individual may participate in the study. The CAPS will serve as the primary outcome measure in this study. The BDI will be a secondary outcome measure to assess symptoms of depression before and after undergoing MDMA-assisted psychotherapy.

The primary outcome measure will be the Clinician-Administered PTSD Scale (CAPS), a clinician-scored measure for PTSD diagnosis and measure of symptom intensity and severity. 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. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability (Blake et al. 1990; Nagy et al. 1993). An independent rater will assess all participants at study baseline and six weeks after the third experimental session. The same independent rater will assess all participants enrolled in stage 2 six weeks after their third open-label session. Any participant undergoing the optional fourth session of MDMA-assisted psychotherapy will have PTSD symptoms assessed six weeks after this session.

The Posttraumatic Diagnostic Scale will serve as an additional measure of PTSD symptoms. The measure was designed to assess PTSD following DSM criteria (Foa et al. 1997; Foa et al. 1993). 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 independent rater will administer the PDS, collect completed measures and score them at baseline and six weeks after the third experimental session. The independent rater will also administer, collect and score the PDS six weeks after the third open-label session for participants enrolled in Stage 2 and six weeks after the optional fourth open-label session.

The Beck Depression Inventory (BDI) is a 21-item a self-report measure of depressive symptoms (Beck and Steer 1984; Beck and Ward 1961) that will serve as a measure of depression. It takes five to ten minutes to complete. Participants will complete the BDI at the same times when the CAPS is administered.

Two measures of cognitive function will be administered at baseline and again six weeks after the third experimental session. The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (Randolph 1998) and the Paced Auditory Serial



Addition Task (PASAT), a measure of information processing speed and efficiency (Roman et al. 1991) will all be administered at these two time points.

All participants will complete measures of PTSD symptoms twice during the study, while participants enrolled in Stage 2 and any participant undergoing a fourth optional MDMA-assisted session will complete measures of PTSD symptoms at additional time points.

1. *Baseline assessment, either at Screening visit or after an appropriate washout period in people taking psychiatric medicines*
2. *Six weeks after Experimental Session 3*

Participants enrolled in Stage 2 complete measures six weeks after open label session 3. Any participant who underwent a fourth optional open-label session will be assessed on PTSD symptoms six weeks after this session. Participants who do not enroll in Stage 2 will not have any additional assessment of PTSD symptoms.

All outcome measures will be administered by an independent assessor. The independent assessor will remain blind to subject condition and will not be present during non-drug or MDMA-assisted psychotherapy sessions.

During the course of each MDMA-assisted psychotherapy session, the Subjective Units of Distress (SUD), a simple, one-item visual analog scale, will be used to assess degree of psychological distress experienced at various points during the session. Participant and investigator beliefs concerning participant condition assignment (either experimental or active placebo MDMA) will be assessed during the non-drug psychotherapy session occurring on the day after each experimental session. Neither the SUD nor condition assignment beliefs measures are outcome measures.

Response to study participation and perceived degree of choice in taking part in the study will be assessed with the Reactions to Research Participation Questionnaire (RRPQ) (Newman et al. 2001). Participants will complete this measure during their final study visit, with exact time of completion varying in accordance with participant enrollment in the open-label study segment or in the fourth open-label MDMA-assisted psychotherapy session. The RRPQ is intended to assess the participant's experience as a research subject, perceived reasons for consenting to be a research participant and perceived freedom to take part in the study, and is not an outcome measure.

All sessions from introductory psychotherapy through weekly integrative psychotherapy and including 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, therapist interventions and for development of a manual of standard procedures for performing MDMA-assisted psychotherapy in people with PTSD.

## **Visit Descriptions**

### **Initial Screening and Diagnostic Evaluation**

Participants will undergo medical and psychiatric screening after giving written informed consent 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, 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. Participants must have a global CAPS score equal to or higher than 50 to be enrolled in the study. Only participants who continue to meet all study criteria without meeting any exclusionary criteria will be enrolled in the study.

### **Subject Numbering**

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at “001”. Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 4-digit subject number. The first two digits identify the study site. The next two digits identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 0401, second 0402, etc.

### **Enrollment and Baseline Evaluation**

Participants will be enrolled in the study if they meet all study inclusion criteria without meeting any exclusion criteria. 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. Any participant taking psychiatric medications at the time of the screening evaluation will be re-assessed after an appropriate washout period of at least five times drug half-life, with the second assessment treated as baseline CAPS values. This is to ensure that an appropriate comparison will be made between baseline symptoms of PTSD and symptoms two months after the second experimental session, when individuals will be medication-free.

### *Randomization*

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. A randomization list will be run to assign either experimental dose or active placebo dose MDMA (125 and 62.5 or 25 and 12.5 mg) MDMA to 12 prescription bottles randomly assigned a number between 1 and 100. The randomization monitor will also create replacement doses that retain the same ratio of experimental dose to active placebo dose condition. The randomization monitor will supervise the procedure of filling bottles with either MDMA or placebo. 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. In all other cases, the blind will be maintained up through the assessment occurring six weeks after the third experimental session. The independent rater and both investigator-therapists will be blind to condition assignment.

### **Psychotherapy**

Participants will undergo a course of psychotherapy consisting of sessions of non-drug, assisted "conventional" psychotherapy and MDMA-assisted psychotherapy. Conventional psychotherapy sessions prior to the first experimental session will prepare participants for MDMA-assisted psychotherapy and help develop a therapeutic alliance with the investigators, and psychotherapy subsequent to MDMA-assisted psychotherapy is intended to integrate and develop experiences participants had during MDMA-assisted psychotherapy. All psychotherapy sessions will be recorded to audio and video. This includes introductory sessions, each experimental or open-label MDMA session and integrative psychotherapy. Participants may upon request receive copies of the audio and/or video recording of their experimental and/or open-label sessions for their own review, and they may also request copies of the audio and/or video recording of their non-drug assisted psychotherapy session recordings.

#### *Introductory Sessions*

The participant will undergo two sixty to ninety minute introductory sessions with the therapist-investigators, who will consist of a male and a female therapist. The investigators will work with the participant to prepare him or her for MDMA-assisted psychotherapy. The investigators and participant will seek to form a strong working relationship with each other, and they will help the participant prepare for upcoming experimental sessions. Introductory sessions will promote a safe space for confronting trauma-related memories, emotions and thoughts. During the third and last introductory session, the investigators will provide participants with instructions listing specific rules and guidelines for food, beverage and drug or medication consumption prior to MDMA-assisted psychotherapy.

#### *MDMA-assisted Psychotherapy*

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 therapist. Procedures for MDMA-assisted psychotherapy will remain the same across each of the two sessions, and all procedures except drug dose will be the same for participants assigned to the full dose and active placebo condition.

Experimental sessions will begin at approximately 10:00 AM and will take place at the offices of the principal investigator, Dr. Ingrid Pacey. The participant will have had

nothing by mouth except alcohol-free liquids since approximately 12 AM on the evening before each experimental session. Participants will arrive at approximately 9:00 AM for collection of a urine specimen that will be used in 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; a positive pregnancy screen is cause for withdrawal from the study. A positive drug screen or failure to follow one or more instruction related to pre-session food or beverage consumption may lead to delaying the session start time, rescheduling the session or withdrawing the participant from the study. The investigators will assess blood pressure and pulse upon arrival and at least twice prior to administering MDMA.

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 SUD 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 dose.

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 (Bonny and Savary 1990; Grof 2000: 1980; Unkefer 1990). After the first hour, if the participant has not spoken spontaneously, the therapist-investigators will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapist-investigators will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging. The therapist-investigators will also encourage periods of time in which the participant remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of their inner experience. Water and electrolyte containing fluids will be available ad lib throughout the session within the limits described under "Monitoring for Toxicity." Food will be available during the latter part of the session. All experimental sessions will be recorded to audio and video in their entirety.

The therapeutic approach during an MDMA-assisted session is non-directive, following and encouraging the MDMA-supported process. Discussions between therapist and participant are only intermittent. The therapists may employ other techniques, including focused body work and anxiety management techniques. Focused body work employs nurturing touch (hand-holding or hugging) and touch aimed at intensifying and thereby releasing body tension and pain by giving resistance for the participant to push against. Focused body work is always performed with explicit consent from the participant and respecting boundaries and vulnerabilities of the patients. Transference is not a main focus and is addressed openly in early stages if necessary. Subsequent MDMA-assisted sessions are expected to lead to deeper emotional experiences, building on the

experiences and results from the previous sessions. MDMA is expected to induce or facilitate the following therapeutic effects and processes: prolonged spontaneous reliving of and confrontation with traumatic memories and emotions; cognitive restructuring, processing of difficult emotions, release of tension and somatic symptoms, increased awareness of past and present positive experiences, new perspectives and changes of meaning.

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. Subjective units of distress (SUDs) will be measured at least once prior to drug administration and 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. If at any time blood pressure exceeds 160 systolic or 110 diastolic, or 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 research site will contain equipment for assessing blood pressure, pulse and body temperature, and for dealing with potential adverse events, such as hypertension, and a means to transport individuals to the nearest hospital in case of a medical emergency. Ambient temperature will be kept comfortably cool to decrease the likelihood of hyperthermia. For more details, see Table 3.

**Table 3.** Schedule of procedures and measures for experimental sessions

<b>TIME</b>	<b>Procedure or Action</b>
9:00	Urine drug screen and pregnancy test. Participant acclimated to environment
9:45	Baseline BP, Pulse, Subjective Units of Distress Rating (SUDS)
9:55	2 <sup>nd</sup> Baseline BP, Pulse, BT, SUDS
10:00	<b>Drug Administration</b> , begin recording to audio and video
10:30	BP, Pulse.
11:00	BP, Pulse, SUDS, BT
11:30	BP, Pulse; <b>Can administer supplemental dose</b>
12:00	BP, Pulse, BT
12:30	BP, Pulse, SUDS
13:00	BP, Pulse
13:30	BP, Pulse, BT
14:00	BP, Pulse, SUDS
Every hour, and as needed	BP, Pulse,
Every 60-90 minutes	SUDS, Temp

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. If the participant agrees to take the supplemental dose, then it will be administered with 250 to 300 mL water or electrolyte-containing beverage. Sessions will last up to eight hours, depending on when the participant feels that he or she has arrived at a point of completion and dependent on the therapists' determination of the mental and physical state of the participant.

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 investigator will discuss with the participant the advantages and pitfalls of a significant other present during the experimental session and will meet and approve the significant other prior to their stay at the study site.

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 near the offices of Dr. Pacey, and both 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 in the offices of Dr. Pacey. With the approval of the therapists, 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 an individual 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. The participant and if applicable, his or her significant other, will receive information that will allow them to contact the investigators during the overnight stay in the case of an emergency or request for additional support. Participants will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

### *Integrative Psychotherapy*

Participants will undergo non-drug psychotherapy on the day after each MDMA-assisted session and on a weekly basis during intervals after each MDMA-assisted session. During these sessions, the therapist-investigators will support the participant as he or she seeks to reach a new perspective and understanding after the experimental session. Expressive techniques such as writing or drawing are encouraged. The therapists will also encourage the transfer of states of acceptance, feelings of intimacy, closeness and reduced fear experienced in MDMA sessions to emotionally threatening everyday situations. The therapist-investigator attitude will be supportive, validating the MDMA experience and facilitating understanding and emotional clearing. Therapists are accessible any time the participant needs support outside the scheduled integration sessions.

### *Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy*

A ninety-minute therapy session with the male and female therapist will take place in the morning of the day after each MDMA-assisted 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. The therapist-investigators will assess participant mental health and the presence of any remaining side effects during integrative psychotherapy immediately after each experimental session. The non-drug psychotherapy session can also serve as an opportunity for the therapist-investigators to gather information about the effects of MDMA on the participant in an unstructured manner. After this psychotherapy session, a person previously selected by the subject will provide a ride home. If the participant is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the participant due to unforeseen events, the investigators will assist the participant in finding an alternative means of returning home.

Prior to integrative psychotherapy, the participant and both therapist-investigators will indicate their beliefs concerning participant condition assignment.

### *Weekly Integrative Sessions*

The participant will have weekly non-drug psychotherapy sessions with both therapist-investigators during the interval between the first and second experimental session, between the second and third experimental sessions and after the third experimental session. Participants will have at least nine 60 to 90 minute integrative psychotherapy sessions prior to the evaluation six weeks after the third experimental session that will signal the end of the randomized study segment. The investigators may conduct more sessions if they and the participant deem it necessary. The participant and investigators will continue to work on supporting the participant as she or he considers his or her experiences during one or both experimental sessions. The investigators will use clinical judgment to assess the participant's psychological well-being during this period of time. If there are any indications of continuing anxiety or distress, 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.

### *Daily Telephone Contact*

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.

### **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 90 to 120 minutes. The independent rater will administer the CAPS and participants will complete the BDI and PDS. The independent rater will administer the RBANS and PASAT. The measures are described earlier in "Assessments and Measures."

### **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 participant will meet with the therapist-investigators for approximately a half hour to an hour and the blind will be broken for the individual participant. The independent rater will remain blind to condition assignment at this time. 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 or the optional open-label session will complete the Reactions to Research Participation Questionnaire (RRPQ) after their final assessment when they have completed the study.

### **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.

#### *Assessment Six weeks after Third Open-Label Session*

All participants in Stage 2 will be assessed by the independent rater six weeks after their final open-label session. The independent rater will assess all participants on the CAPS and participants will complete the PDS and BDI, and the RRPQ.

### **Additional Open-Label Session for Partial Responders and Non-responders**

If the investigators conclude that a participant is responding poorly or not at all after receiving three experimental doses either initially or as part of Stage 2, then they can offer a fourth MDMA-assisted psychotherapy session. The fourth session will be open-label and will occur after a single non-drug psychotherapy session with the investigators. The sequence of events and procedures occurring before, during and after this fourth session will be nearly identical to those occurring in the randomized and open-label study segments. If it seems appropriate and the participant agrees to it, the investigators can administer 150 mg followed by a supplement of 75 mg 1.5 to 2.5 hours after the initial dose. PTSD symptoms and symptoms of depression will be assessed six weeks after this fourth open-label session.

**Removal of Subjects from Therapy or Assessment**

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.

The subject will be clinically monitored after withdrawal, the cause of which will be recorded on the "Study Termination" CRF. Where the withdrawal of a subject resulted from an adverse event, this will be documented in accordance with the procedures in section.

Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out.

**Premature Discontinuation of the Study**

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform the study subjects and will assure appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor, will be treated in accordance with federal and local regulations.

**Data 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 (ANOVAs) with condition (active placebo versus experimental) 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 that will examine 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. They will perform a correlational analysis examining the relationship between PDS score and BDI scores at each time of administration.

The investigators will examine the effects of active placebo versus experimental dose MDMA-assisted psychotherapy 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 experimental 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.”

If any subjects receive a fourth session, the assessments after the fourth session will be compared with all prior post-baseline assessments.

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.

Descriptive statistics will be computed for 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.

### **Statistical power**

The proposed study is a pilot investigation intended to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with PTSD. Because of their exploratory nature, pilot studies are often underpowered for detecting the desired effect. Because it is a pilot study in a small sample, statistical power is difficult to assess but it is likely to be low. However, preliminary analyses of MAPS’ almost completed US study of MDMA-assisted psychotherapy in 21 people with PTSD has produced promising results and suggests a medium effect size with respect to treatment efficacy. Hence estimated effect size may follow between 0.5 and 0.7. The sponsor intends to use preliminary data gathered from this and other studies in part to guide future estimates of effect size and statistical power in future studies. The sponsor intends to conduct meta-analyses of CAPS scores gathered across all pilot-studies in addition to analyses of individual study data. Meta-analyses will be able to increase overall statistical power.

The sponsor used Java applications created by Lenth and posted on the website listed below to calculate estimated statistical power for this study, assuming an effect size of 0.6 for the impact of two sessions of MDMA-assisted psychotherapy on symptoms of

PTSD and depression (Lenth 2006). We initially conducted a two-sample independent t-test comparing one group of eight and another of four with effect size set at 0.6 and with equal sigma (estimated standard deviation) assumed and set at 1. The software calculated an estimated power of 0.144, indicating an underpowered study. After taking into account preliminary analyses of CAPS scores occurring in the randomized, placebo-controlled study of MDMA-assisted psychotherapy taking place in South Carolina, we conducted a second estimate assuming a larger effect size of 0.8, reaching estimated statistical power of 0.22.

### **Monitoring for Toxicity**

There is now a considerable body of information indicating that the likelihood of significant toxicity from the doses of MDMA used in a therapeutic setting is very low (Baggott et al. 2001; Dumont and Verkes 2006; Jerome 2004; 2005; 2007). 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 drug-related serious adverse events occurring during sessions (Adamson 1985; Gasser 1994; Greer and Tolbert 1986; Metzner and Adamson 2001; Widmer 1998). There have been no drug-related serious adverse events during the course of a study of MDMA-assisted psychotherapy in 21 people with PTSD under the direction of Dr. Mithoefer, nor in MAPS' Swiss MDMA/PTSD study with six subjects or in MAPS' Israeli MDMA/PTSD study with one subject having completed the study.

Recent findings in humans and nonhuman primates have failed to find any significant interactions between ambient temperature and body temperature in humans receiving 2 mg/kg MDMA (Freedman et al. 2005; Von Huben et al. 2006), a finding in line with inconsistent results concerning elevation of body temperature after MDMA (de la Torre et al. 2000c; Fantegrossi et al. 2004; Farre et al. 2004; Johanson et al. 2006; Liechti et al. 2000a). These findings suggest that unlike rodents, extreme elevation in body temperature after MDMA is rare in humans, likely due to differences in rodent and primate thermoregulation.

Although the safety data is reassuring, we intend to monitor closely for the unlikely possibility of an untoward reaction. The sessions will be conducted in a psychiatric office where basic emergency equipment will be immediately available. The site is 5 minutes from two nearby hospitals with emergency departments, University of British Columbia Hospital and St. Paul's. Both hospitals are accessible during the day, while only St. Paul's remains accessible for 24 hours. Participants will be sent to whichever emergency department is accessible in case of a medical emergency.

#### *Hypertension and related cardiovascular Effects*

Blood pressure and pulse will be measured at regular 30-minute intervals (see table 3). 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. During this time the principal investigator will continually

evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. The principal investigator will make a clinical judgment about whether additional monitoring or treatment is required. Reasons for moving a patient to an emergency department would include, but not be limited to, severe headache in the setting of hypertension, angina or neurological deficits regardless of blood pressure. The investigator may, at any time, make a clinical judgment to transfer the participant to the emergency department for closer monitoring and additional treatment. If such transfer is required a team of paramedics would be summoned to transfer the subject to the nearest hospital by ambulance.

*Angina or Myocardial Infarction:*

The investigators will observe the participant and note any complaints of chest pain. If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, paramedics will be summoned to stabilize the subject by administering oxygen and any other appropriate drugs or resuscitative measures within their scope of practice. The paramedics will start an IV and cardiac monitoring and transport the subject to a nearby hospital where appropriate further evaluation and care can be given. If further evaluation at the hospital reveals that the participant has had an acute myocardial infarction (AMI), he or she will be well within the time frame required for definitive therapy.

*Stroke:*

The investigators will attend to any signs or symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress. If any participant has neurological deficits, whether or not they are associated with hypertensive crisis, he or she will receive further care by paramedics and transport to a nearby hospital as described in the above section on Angina or Myocardial Infarction.

*Psychological Distress:*

During preparatory sessions, participants will be made aware of the fact that difficult emotions, including fear, panic, grief or rage, may arise during experimental sessions. They will be told that such symptoms will not be treated pharmacologically during the sessions because they present 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, then the principal investigator may prescribe a benzodiazepine or other anxiolytic drug, as zolpidem.

The potential for destabilizing psychological distress will be minimized by excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders), by preparing people before the experimental session, by creating an atmosphere of trust during the experimental session, by close monitoring, by daily contact with subjects for the period of a week after the

experimental session, and by providing non-drug integrative psychotherapy sessions. Participants will remain in the offices of Dr. Pacey for the night after each experimental session. The investigator will be able to attend to the participant if there is a need to deal with continued psychological distress.

If, by the end of an MDMA-assisted psychotherapy session, the participant is still severely agitated or experiencing great psychological distress, the following measures will be taken:

- If a participant is anxious, agitated, in danger of any self harm or is suicidal at the end of the experimental session, the investigators will remain with the participant for at least two more hours. During this time, the investigators will employ affect management techniques described in the treatment manual draft under development for MDMA-assisted psychotherapy in people with PTSD (Ruse et al. 2005), will talk with the participant to help him or her gain cognitive perspective of their experiences, and will help them implement the self soothing and stress inoculation techniques they were taught in the introductory sessions. If this situation should occur at the end of one of the ninety-minute follow-up sessions at least one of the investigators will be available to stay with the participant for at least two additional hours.

- If a participant remains severely anxious, agitated or in danger of self harm or suicide, or is otherwise psychologically unstable at the end of this two hour stabilization period, the principal investigator may undertake one of two options:

A. The attendant will stay with the participant until the time of his or her appointment with the investigators the next day. The investigators will then meet with the participant daily until the period of destabilization has passed. At any time during this process, Dr. Pacey may make the clinical judgment to proceed to option B.

#### B. Hospitalization for stabilization

Participants hospitalized after a severe panic reaction will be suspended from study participation until after recovery or stabilization, at which time the investigator will carefully evaluate the participant's emotional status. If this response occurs during the first experimental session, the investigator may elect to forego the further experimental sessions and drop the participant from the study. This decision will be made after discussion with the IRB and any other appropriate regulatory agencies.

For those participants engaged in an on-going therapeutic relationship, the investigators will actively involve the participant's outside therapists in the management of any psychiatric complications of treatment.

In the event that a participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an experimental session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." If a participant should become psychotic or suicidal, arrangements will be made for him or her to be admitted to the nearest inpatient psychiatric facility of their choice. Residual

symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Any participant who develops mania or psychosis will not be given a further MDMA session and will receive appropriate psychiatric treatment.

*Hyperthermia:*

The investigators will assess 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 as described above under Angina or Myocardial Infarction.

*Dehydration:*

Study participants will not be engaged in strenuous exercise and are not expected to be sweating profusely during experimental or open-label sessions. However, participants will have access to water and electrolyte-containing beverages throughout these sessions and the investigators will encourage participants to drink fluids if they observe very little fluid consumption within three to six hours, and noting participant activity, degree of water loss through sweat and body temperature.

*Hyponatremia:*

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 for evaluation as described in the above section on Angina or Myocardial Infarction.

If a participant exhibiting signs of clinically significant hyponatremia is sent to a hospital and testing finds that he or she has low serum sodium during an experimental session, then the principal investigator will not enroll the participant in any subsequent experimental or open-label sessions.

*Liver toxicity:*

Liver enzymes will be measured as part of the initial screening visit. Volunteers with pre-existing abnormalities will be excluded from the study. 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:*

On the basis of findings from research in humans and nonhuman animals and considering the setting of use, the likelihood for abuse or dependence on MDMA triggered by participation in this study is very low (see “Abuse Potential” below). The investigators will exclude all participants meeting the criteria for substance abuse or dependence 60 days prior to screening. 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.

**Medical Emergencies**

The study site will contain equipment for assessing blood pressure, pulse and body temperature and there will be an automatic external defibrillator (AED) on site. Dr. Pacey will maintain basic life support (BLS) certification or its equivalent in Canada in cardiopulmonary resuscitation (CPR) including training in using an AED. The site is 5 minutes from either the University of British Columbia emergency department or from St. Paul’s Hospital emergency department. In the event of a medical emergency paramedics will be summoned and study subjects will be transported by ambulance to either hospital as appropriate. We consider this to be an adequate level of emergency back-up based on experience with previous phase II studies in the US and Switzerland during which there have been no adverse events during experimental sessions requiring emergency care or any other medical intervention.

The first US phase II trial with MDMA to be completed in September, 2008, was conducted in an outpatient setting with a “crash cart” of emergency equipment on hand and an emergency physician and nurse in the building. The estimated transport time from this site to the nearest hospital emergency department was approximately ten minutes with an estimated response time for an emergency medical services ambulance of approximately eight minutes. In this study MDMA was administered on 51 different occasions at a dose of either 125 mg. by mouth or 125 mg. followed in 2 – 2.5 hours by an additional 62.5 mg. Blood pressure, pulse and temperature were closely monitored, but never reached levels that required intervention, nor were there any other medical problems requiring treatment during the MDMA sessions. Subsequently a similar study has been approved in Switzerland and is being conducted in an outpatient psychiatry office approximately 5 minutes from the nearest hospital without a crash cart or emergency personnel on site. As of this writing the Swiss investigators have administered



125 mg followed by 62.5 mg MDMA on 20 occasions and administered 150 mg MDMA on two occasions without medical incident.

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event. All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:

Mild: no limitation in normal daily activity.

Moderate: some limitation in normal daily activity.

Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

#### 1. Not Related

The AE is not related if exposure to the investigational product has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition.

#### 2. Possibly Related

The administration of the investigational product and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational product.

#### 3. Probably Related

Exposure to the investigational product and AE are reasonably related in time **and** the investigational product is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

The relationship of the study treatment to an AE will be determined by the investigator.

### **Serious Adverse Events**

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

Results in death

Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.

Requires or prolongs inpatient hospitalization

Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)

Results in a congenital anomaly/birth defect

Requires intervention to prevent permanent impairment or damage

Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as **non-serious**. It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as an on study SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

### **Adverse Event Collection**

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 of the following:

**Medical Monitor:** Michael C Mithoefer [Mmit@bellsouth.net](mailto:Mmit@bellsouth.net)

843-849-6899

**Study Monitor:** Valerie Mojeiko [Valerie@maps.org](mailto:Valerie@maps.org); 831 336 4325

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

- Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions.
- Any adverse event leading to withdrawal from the study.

Additional adverse events collected for seven days after each experimental session are:

- Common side effects.
- Exacerbation of anxiety.

### **Collection of Concomitant Medications**

All prescription concomitant medications will be recorded at baseline. The investigators will keep track of any newly initiated medications taken during the course of the study, including herbal or nutritional supplements. Only newly initiated medications will be recorded after baseline.

### **Laboratory Assessments**

Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. 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.

### **Study Monitoring, Auditing and Documentation**

Investigators and/or their study staff will be trained during the initiation visit. During each monitoring visit, source data verification will be performed by qualified staff representing the sponsor who will visit the offices of Dr. Pacey. Monitoring visits will occur every six to 12 months (26 to 52 weeks). A CRF collation supplied by the sponsor will be completed for each subject. The entries will be checked by trained delegates of the sponsor.

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.

## **Risks and Discomforts**

### **Risks and Discomforts Associated with Drawing Blood**

Blood specimens will be obtained from the subjects during baseline evaluation. Temporary discomfort may arise as a result of sampling blood. Participants may experience temporary discomfort at the blood drawing site. There is also a remote possibility of inflammation or infection at the blood drawing site. Blood samples will be used for the most part to determine whether the participant is healthy and can safely take part in the study. Hence the temporary discomfort is outweighed by the need to ensure that participants are healthy, meet all inclusion criteria at screening, or are not experiencing any changes in condition prior to entering open-label study segments.

### **Risks and Discomforts Associated with Screening Procedure**

Medical data will be collected via history and physical examination and measurement of vital signs. Submitting to a full medical examination may be time consuming, and may be distressing or uncomfortable for some. Because medical examinations are part of the screening procedure, they cannot be omitted from the study design.

Psychological assessments will be obtained through interviews. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of PTSD symptoms are used during screening, they cannot be avoided. The investigators have experience working with people with PTSD, and they will seek to reduce anxiety and distress during these interviews.

### **Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy**

During non-drug and MDMA-assisted psychotherapy sessions, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy, experimental and open-label sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention (MDMA-assisted psychotherapy), and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

All psychotherapy sessions will be recorded to audio and video. Participants may feel uncomfortable with having their sessions recorded. The recordings will be used for developing a manualized form of MDMA-assisted psychotherapy, and participants may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment. Participants will receive information on who will have access to recordings and will have control over any presentation of this material beyond viewing by investigators or regulatory agencies.

## **Risks and Discomforts of Receiving the Study Drug (MDMA)**

Side effects of MDMA are modest and have generally not been associated with serious discomfort by volunteers in previous studies (Baggott et al. 2001). Decreased appetite, jaw clenching, dry mouth, impaired gait or balance and impaired concentration are commonly reported during peak MDMA effects, while fatigue may be felt up to several days afterward. Less commonly, mild anxiety and depressed mood are reported one and three days after MDMA administration (Harris et al. 2002; Liechti et al. 2001; Liechti et al. 2005; Liechti and Vollenweider 2000a; b; Vollenweider et al. 1998). Commonly reported side effects reported by Mithoefer in participants who received the experimental drug while undergoing MDMA-assisted psychotherapy also included neck and back pain and diarrhea. Some of these effects are very likely to occur, but proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects, so that they will not be unduly troubled by them. Other common side effects are listed in the Investigator's brochure.

### *Cardiovascular and Sympathomimetic Effects*

In doses similar to those proposed for this study, MDMA produces sympathomimetic effects similar to the effects of a moderate dose of methamphetamine or other stimulants (Cami et al. 2000b; Grob 2001; Grob et al. 1996; Harris et al. 2002; Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2003). The amount of MDMA used in all experimental conditions in this study is not likely to produce changes in blood pressure or heart rate greater than 40% of resting values. These changes should last no more than six hours. These changes have been well-tolerated by volunteers in previous studies and should not pose large risks to participants who have been carefully screened for cardiovascular and related problems. In less than 5% of volunteers in phase 1 studies, increases in blood pressure were higher. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of participants and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity.

The higher dose of MDMA available during open-label sessions has been administered in research settings (de la Torre et al. 2000a; Freedman et al. 2005), and an investigator in Switzerland has administered it twice in the course of his research in people with PTSD (Oehen 2008b). This dose may produce greater elevations in blood pressure and greater subjective effects, though the elevation, with maximum values over the threshold for requiring more frequent assessment, but with average elevation not much higher than after 125 mg (Oehen 2008b, personal communication). The investigators will offer the higher dose if they believe that it may benefit the participant without causing any harm.

### *Perceptual Alteration*

MDMA may produce mild alterations in perception and altered perception of time (see for example Cami et al. 2000b; Dumont and Verkes 2006; Vollenweider et al. 1998). Women may be more sensitive to these effects of MDMA (Liechti et al. 2001).

### *Psychological Distress*

Some participants receiving MDMA report experiencing periods of increased anxiety (Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003). It is possible for psychological distress after MDMA to arise from the first indications of drug effects up until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress may last for as little as 15 minutes or for as long as 5 hours. In previous Phase I studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from investigators. In the proposed study, participants will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. Investigator responses to psychological distress is discussed in detail in “Monitoring for Toxicity.”

Less commonly, people report experiencing mild anxiety and depressed mood one and three days after MDMA administration (Baggott et al. 2001; Harris et al. 2002; Huxster et al. 2006). At least some of the physiological or psychological side effects listed above are very likely to occur. Proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects, so that they will not be unduly troubled by them.

### *Immunological Changes*

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. A research team in Spain has studied the acute immunological effects of one or two doses of 100 mg MDMA (Pacifici et al. 2004; Pacifici et al. 2000; Pacifici et al. 2001a; Pacifici et al. 1999b). They reported a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon- $\gamma$  and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings (Connor 2000; Connor II). Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine (Pacifici et al. 2000; Pacifici et al. 2001). Because of their limited duration, these changes are not likely to have clinical significance beyond an increased risk of the common cold or similar illness for several days. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose (Pacifici et al. 2001a; Pacifici et al. 2002), and a second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose (Pacifici et al. 2002). Given this data, it is possible that administering a smaller supplemental dose 2.5 h after the first dose will slightly enhance

the immunological effects set in motion by the first dose. Previous Phase I studies have not reported any indication of increased risk of illness occurring after MDMA administration. The investigators will use clinical judgment when considering enrolling participants who are otherwise immunocompromised. It is notable that at least some anti-retrovirals produce dangerous interactions with MDMA.

### *Toxicity*

Serious MDMA toxicity is rare even in uncontrolled settings, considering that millions of users taking ecstasy of unknown identity, potency, and purity with many users consuming estimated MDMA doses that are several times higher than those used in the proposed study without any apparent toxicity (Baggott et al. 2001). Under unsupervised and non-medical conditions, the most common serious adverse event involves hyperthermia, described above in “Monitoring for Toxicity” (Liechti et al. 2005; Williams et al. 1998). This event has not occurred during controlled studies of MDMA. A comparison of findings in humans with those in rodents suggests that rodents are more sensitive to elevation in body temperature after MDMA (Gordon 2007). In addition to hyperthermic syndromes, other rare adverse events include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia. In the proposed clinical study, volunteers will be excluded on the basis of any conditions that might increase risk of their occurring and/or will be carefully monitored for signs and symptoms of these unlikely events.

### *Potential Neurotoxicity Associated with Ecstasy Use*

Extensive studies in animals indicate that high or repeated doses of MDMA can damage serotonergic axons originating in the brainstem dorsal raphe nucleus, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site density (Cole and Sumnall 2003b; Green et al. 2003; O'Callaghan and Miller 1994), with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin (Hatzidimitriou et al. 1999). Similar changes can be induced by methamphetamine and other psychostimulants (Miller and O'Callaghan 1996; Molliver et al. 1990; Sabol et al. 1995; Seiden and Sabol 1996). Previous studies in nonhuman primates overestimated human-equivalent doses (Mechan et al. 2006), and previous studies in rodents may also have overestimated human-equivalent doses (Baumann et al. 2007). Studies in rodents and monkeys that employed lower or fewer doses of MDMA, or that involved self-administration, have failed to find some or all of the markers of serotonin neurotoxicity listed above (Banks et al. 2008; Fantegrossi et al. 2004; Wang et al. 2005; Wang et al. 2004). Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials (McCann and Ricaurte 2001). However, they are basing their case on studies that employed inappropriately high doses of MDMA, and studies comparing the effects of repeated use of ecstasy, often along with other drugs, as discussed below.

There is controversy as to whether analogous changes in brain serotonin occur in humans, and a wealth of literature exists that compares ecstasy users to non-users (Cole and Sumnall 2003a). Earlier studies were retrospective and possessed a number of methodological flaws, particularly in relation to appropriate matching of ecstasy users with controls. Later research employed longitudinal study designs, allowing for

comparisons over time. Retrospective and longitudinal imaging studies have detected decreased estimated serotonin transporter (SERT) sites in current heavy ecstasy users when compared with controls (McCann et al. 2005; Reneman et al. 2006a; Thomasius et al. 2006), but with estimated SERT sites returning to normal or numbers inversely related to period of abstinence. Likewise, studies have detected impaired memory and executive function in ecstasy users (Cole and Sumnall 2003a; Laws and Kokkalis 2007; Zakzanis et al. 2007). A number of these studies reported impaired cognitive function only in heavy users, and not in moderate users, and some recent studies suggest that use of other drugs may contribute to impaired cognition (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hoshi et al. 2007; Roiser et al. 2007), though other studies also reported that abstinence from ecstasy did not attenuated memory impairment in heavy users (Gouzoulis-Mayfrank et al. 2005; Thomasius et al. 2006). There is also some evidence that ecstasy users are more likely to report symptoms of anxiety or depression, and to exhibit more behavioral impulsivity than non-ecstasy user controls (Daumann et al. 2004; Morgan et al. 2006; Sumnall and Cole 2005; Sumnall et al. 2004). Findings from prospective and longitudinal studies suggest that young people with existing psychological problems are more likely to try ecstasy than people without these problems (Huizink et al. 2006; Lieb et al. 2002), and it appears that polydrug use may contribute to this association (Daumann et al. 2004; Medina and Shear 2006; Scholey et al. 2004; Sumnall et al. 2004). Findings from retrospective studies are of limited value in estimating the potential risk of neurotoxicity from two doses of MDMA, as average cumulative dose and frequency of use in most of these studies is considerably higher than doses in human trials of MDMA. A better estimate of the potential risk of neurotoxicity can be found in findings from prospective studies comparing people before and after their first use of ecstasy.

Starting in the early 2000s, a team of researchers in the Netherlands examined samples of people before and after reporting their first uses of ecstasy. These researchers have assessed estimated SERT sites, chemical markers of neuronal injury, changes in cerebral blood flow, performance and brain activity related to a working memory task, and cognitive function in samples of ecstasy users reporting an average use of 1 to 3 tablets (De Win 2006; de Win et al. 2007; Jager et al. 2007b; Schilt et al. 2007). The team also performed studies expressly in heavy ecstasy users (de Win et al. 2004; Jager et al. 2007a; Reneman et al. 2006b). They failed to find reductions in SERT sites, signs of neuronal injury, changes in working memory task performance or brain activity when performing this task in samples reporting use of no more than six ecstasy tablets (de Win et al. 2007; Jager et al. 2007b). They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else, and they failed to find any markers of neuronal injury (de Win et al. 2007). Low use of ecstasy also failed to alter brain activity or performance on a measure of working memory (Jager et al. 2007b). When comparing cognitive function in people before and after their first use an average of 3.2 tablets and non-user controls at similar points in time, ecstasy users showed less improvement on a memory task than non-users (Schilt et al. 2007). It is notable that the study examining SERT sites and cerebral blood flow did not employ non-user controls, and that all participants in the study of cognitive function performed within the normal range, and that one individual had reportedly used ecstasy on 30 occasions rather than the limit of 10



occasions set for the other studies. Taken together, their findings fail to confirm serotonergic neurotoxicity after low ecstasy use, yet found some possible indications of impaired memory.

We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. Nevertheless, the risks of neurotoxicity arising from MDMA administration will be described and noted in application materials prior to and during the completion of the application. Cognitive function will be assessed at baseline and again six weeks after the third double-blind session, and the investigators will informally monitor for any signs of changes in cognition after each MDMA-assisted session.

### *Abuse Liability*

MDMA is classified as a Schedule I compound, largely on the basis of its growing popularity at night clubs and parties in the early to mid-1980s. MDMA possesses abuse liability, and this is discussed in “Additional information.” Whether or not MDMA's abuse potential will negatively affect people with PTSD exposed to MDMA when given along with psychotherapy is an open question for which there is of yet no direct data. Mithoefer and colleagues are in the process of conducting a long-term follow-up of participants who took part in the study of MDMA-assisted psychotherapy that will address this question. Mithoefer reported that anecdotally it appeared that people did not develop problems with MDMA/ecstasy abuse and that a number of participants volunteered that they would never seek out ecstasy outside a legal, controlled therapeutic setting. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions and memories related to the original traumatic incident in addition to or even instead of increased positive mood or euphoria. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings. Diversion is not an issue because MDMA will only be administered under the supervision of the principal investigator and no take-home doses will be permitted. More information on the abuse liability of MDMA can be found in “Additional Information.”

### *Reproductive and Developmental Risks*

Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association, as discussed below in the “Pharmacology” section and in pp. 29-30 in the Investigator’s brochure (Bateman et al. 2004; McElhatton et al. 1999). Pregnant women will be excluded from participation in the proposed study, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each client-role session and must agree to using birth control during the period of the study.

### **Risks and Discomforts of Receiving the Active Placebo Dose of Study Drug**

Receiving the active placebo doses of 25 mg MDMA followed 1.5 to 2.5 hours later by 12.5 mg MDMA may be associated with some of the risks above but to a far lesser degree. People receiving low doses of MDMA report only a few subjective effects and do not exhibit significant cardiovascular changes (Grob et al. 1996). It is possible that the addition of the supplemental dose will produce slight increases in positive and negative mood and slightly elevate blood pressure, as reported after administering approximately 35 to 40 mg (Harris et al. 2002). The active placebo dose of MDMA is not expected to produce most or all of the potentially therapeutic effects of the drug, such as increased positive mood, facilitated recall and changed perception of meaning, and increased feelings of closeness to others. Hence people receiving active placebo may experience a lesser reduction in PTSD symptoms from MDMA-assisted sessions.

### **Alternative Treatments and Procedures**

The alternative to participating in the research study is to decide not to take part in the study. The decision not to participate in this research study will not in any way alter or compromise the care offered to individuals receiving therapy from the investigator or any physician involved in this research study.

The investigators will discuss alternatives to study participation, including other available treatments, with all potential participants. There are a number of recognized treatments for PTSD. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatments for PTSD include anxiety management (stress inoculation training), cognitive therapy, exposure therapy and psychoeducation. Psychodynamic psychotherapy and Eye Movement Desensitization and Reprocessing are also used to treat PTSD.

Drugs available in Canada for treating PTSD include paroxetine, and in the US only Sertraline and paroxetine are approved for use in treatment of PTSD. Sertraline has been shown to decrease the hyperarousal and avoidance symptoms, but not the re-experiencing symptoms, of PTSD. Paroxetine has been shown to have an effect on all three categories of symptoms in approximately 62 % of patients. Other medications commonly used are other SSRIs, nefazodone, venlafaxine, tricyclic antidepressants, benzodiazepines, buspirone, zolpidem and mood stabilizers.

### **Confidentiality**

Every effort will be made to strictly safeguard the confidentiality of all participants. Despite this, privacy cannot be guaranteed. Data collected from each participant will be identified only by the participant's initials on the source document and by a randomly generated numeric code on all secondary documents and databases. The investigators will retain a key associating these new numbers with those assigned to participants upon study enrollment. All measures, records, audio and video recordings will be kept in a locked file drawer in a locked office. Access to measures will be limited to regulatory agencies, researchers assessing the participant for changes in symptoms, and individuals analyzing

data. Researchers with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Participants will sign forms for the release of information to any of the individuals who will need to obtain this information. Interested parties might include the prescribing physician or psychiatrist.

Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. While it is possible that individuals may be identified on audiotope or video recording through means other than their names, restricting access to audiorecordings or video recordings greatly reduces the opportunity for identification.

### **Costs to Participants**

There will be no costs to participants for any study-related procedures. The sponsor (MAPS) will pay for all assessments, laboratory work or physical examinations needed to determine study eligibility. The sponsor will also cover costs of the study drug and remaining at the study site on the night after each MDMA-assisted psychotherapy session. The sponsor will pay for all study drugs and study procedures. The sponsor will cover all costs for travel, food and lodging. Travel cost will include air fare for an economy class ticket to the study site if necessary and will include train or parking costs. Participants will not be paid for their participation in this study.

### **Risk/Benefits Analysis**

Developing an array of potential treatment options for PTSD will increase the likelihood of symptom reduction and recovery in people with this debilitating psychiatric disorder. MAPS intends to develop MDMA-assisted psychotherapy as one such treatment. If efficacious, this treatment could require fewer visits with psychotherapists and less use of daily medication. MDMA-assisted therapy may help people whose PTSD symptoms persist despite treatment with established psychotherapies and pharmacotherapies. The sponsor has supported one investigation that is almost complete in the US, and investigations that are now underway in Switzerland and Israel. If results from these Phase II studies, including the proposed study, are promising, then MAPS will embark upon Phase III investigations at multiple sites.

Administering the study drug exposes study participants to a number of potential risks and discomforts that would not otherwise occur. The experimental dose of MDMA is liable to produce common physiological and psychological side effects during each experimental dose MDMA-assisted session, such as increased blood pressure or elevated anxiety. People with PTSD receiving MDMA within a therapeutic setting may very well experience strong negative emotions during the session, as fear, rage or grief. There are reports of a number of serious adverse events in people in uncontrolled, non-medical settings after taking ecstasy. However, there is good evidence that conducting three separate experimental sessions administering initial doses of 125 mg followed by 62.5

mg MDMA in a clinical setting poses a low risk to participants. Conference presentations of data from a controlled study and prospective studies of people before and after ecstasy use have found little to no differences in brain activity and serotonin system function (de Win et al. 2007; Ludewig S et al. 2003; Vollenweider and Scherpenhuyzen 2000). A preliminary data analysis of cognitive function at baseline and two months after the second experimental session in the study of MDMA-assisted psychotherapy in 21 participants failed to find any significant differences between participants who received two doses of MDMA and participants who received placebo (Wagner 2008). However, one prospective study comparing cognitive function before and after ecstasy use found differences between ecstasy users and non-users (Schilt et al. 2007). When tested a second time an average of eleven months later, people who had not used ecstasy improved their performance on a verbal memory task, while people who used ecstasy did not improve performance on this task. However, it is notable that at least one participant reported use of 30 tablets and all participants performed within the normal range. As well, other studies have failed to find impaired memory or decision-making in moderate ecstasy users, with moderate use often defined as below 50 tablets or occasions of use (Back-Madruga et al. 2003; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Medina et al. 2005). Hence it is very unlikely that the dosing and schedule of sessions proposed in this study will result in impaired verbal memory.

One research team reported discontinuing use of 150 mg MDMA after noting an increase in cardiovascular effects and a greater number of unwanted side effects (de la Torre et al. 2000), and studies in ecstasy users suggest increasing risk of detectable impairment in cognitive function with increasing cumulative lifetime exposure. However, there are previous studies that employed designs involving four separate administrations, one per session (Ramaekers and Kuypers 2006), and a human MDMA study employing milligram per kilogram doses close to 150 mg failed to report difficulties after this dose (Freedman et al. 2005). Participants in this study can, if they wish and with the mutual agreement of the investigators, decline the last open-label session available to them, thus allowing for some control over number of treatments that is responsive to the condition and health of the participant. Investigators will only offer a higher dose of MDMA if they believe it will not cause harm and may provide the participant with benefits, and the participant may decline the higher dose. The investigators will observe response to higher doses with care and they have the discretion to increase monitoring vital signs or psychological distress after higher doses. Since administering the supplement is at the discretion and agreement of investigator and participants, the potential for increased risks will be reduced through refraining from using the supplement if response to the initial dose is strong or produces notable increases in cardiovascular effects or side effects. At least some reports suggest inter-individual responses to the same dose, including doses matched milligram per kilogram (Harris et al. 2002), and a recent report in press suggests inter-individual differences in metabolism (Kolbrich et al. 2008). The sponsor and investigator will use data gathered from the proposed study and other studies to develop a schedule of MDMA-assisted psychotherapy that is optimally beneficial with the least number of exposures, reducing the time cost and increasing the affordability of the treatment. Providing an opportunity to use at least one higher dose will assist in locating the optimal dose or range of doses for MDMA-assisted therapy. Despite the increase in

risks for acute and long-term effects after MDMA, the risks of an increased number of exposures and higher doses remain low.

A third of the study participants will receive an active placebo dose of MDMA. The initial and supplemental doses to be used in the active placebo condition were chosen to produce only a few of the subjective effects of MDMA. While the active placebo dose is hypothesized to have little to no therapeutic benefit, it will also produce fewer and less strong side effects and is associated with lesser cardiovascular effects. Study participants in the active placebo condition will receive a course of non-drug therapy along with the MDMA-assisted sessions. All participants in this study will have the opportunity to undergo three sessions and perhaps a fourth with fully active doses of MDMA. Active placebo participants can enroll in Stage 2, which will be identical in structure and scheduling to sessions received during the randomized study segment. An active placebo group is required in order to properly assess the efficacy of study drugs, and an active placebo is required when dealing with psychoactives such as MDMA. Because MDMA produces a unique array of effects, the investigators will use a lower dose of the study drug that may produce enough of these effects to be a credible active placebo.

After taking into consideration the costs and benefits associated with the current study versus alternative treatments available for people diagnosed with PTSD, we conclude that the benefits of conducting the proposed study outweigh the risks, as the risks are minimal and the investigators will further reduce these risks through careful screening and monitoring of study participants. If MDMA-assisted psychotherapy is found to be efficacious, it has the potential to improve the lives of people with PTSD.

### **Chemistry, Manufacturing and Control Information**

The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula  $C_{11}H_{15}NO_2$ . The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by Prof. Dr. R. Brenneisen, DCR, University of Bern, Switzerland. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94. 1 B5.5 with no decomposition products detectable and a HPLC purity >98%.

The encapsulation will be performed by an individual possessing the appropriate skills, as a pharmacist. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, mannitol or a similar inactive compound used to ensure that all capsules have similar weights. The lowest dose contained in one capsule will be 12.5 mg, which is the supplemental dose offered to participants in the Active Placebo condition, and the highest dose contained in one capsule will be 150 mg, which is the higher initial dose that can be used during two

open-label sessions. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent investigators and participants from distinguishing contents of Active Placebo and Experimental Dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging as either being 125 and 62.5 or 150 and 75 mg. Bottles will contain both initial and supplemental doses.

MDMA will be handled in accordance with all provincial and national regulations and forms pertaining to the use of controlled substances in Canada, and will be maintained by the investigators. The MDMA will be stored in a locked safe and only the therapist-investigators will have access to the drug product. All doses will be prepared in a manner to ensure that the investigators cannot distinguish between Low and Fully Active dose capsules.

## **Pharmacokinetics and Pharmacodynamics**

### **Primary Pharmacology**

The compound to be used in this study is racemic 3,4-methylenedioxymethamphetamine (MDMA). This ring-substituted phenylisopropylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor (Battaglia et al. 1988; Setola et al. 2003; Verrico et al. 2007). Its direct actions on serotonergic, adrenergic and other receptors is considerably lower.

MDMA interacts with plasma monoamine transporters and storage vesicles to increase extracellular levels of serotonin (5-HT), dopamine, and norepinephrine (Cozzi et al. 1999; Fitzgerald and Reid 1990; Hiramatsu and Cho 1990; Kankaanpaa et al. 1998; Nash and Brodtkin 1991; Rudnick and Wall 1992; Schuldiner et al. 1993). Direct MDMA stimulation of postsynaptic 5-HT<sub>2A</sub> receptors and  $\alpha$ 2 adrenoceptors also contributes to MDMA's effects (Gudelsky 1996; Koch and Galloway 1997; Palfreyman et al. 1993; Schmidt et al. 1992; Yamamoto et al. 1995). For example, dopamine release is also indirectly increased by MDMA stimulation of 5-HT<sub>2A</sub> receptors on GABAergic striatonigral neurons (Yamamoto et al. 1995).

Although the specific mechanisms of MDMA's therapeutic effects are not fully understood, several observations and hypotheses can be made. The direct and indirect effects of serotonin release may make a large contribution to producing the subjective effects of MDMA, as pre-treatment with SSRIs reduces most or all the drug's subjective and physiological effects (Farre et al. 2007; Liechti et al. 2000a; Liechti and Vollenweider 2000b; Tancer and Johanson 2007), with one study reporting reductions in sociability (Farre et al. 2007). Indirect effects of serotonin release of potential significance include indirect activation of 5HT<sub>1A</sub> receptors and elevating the neurohormone oxytocin (Thompson et al. 2007). Studies in rats reported that stimulating 5HT<sub>1A</sub> receptors attenuated aggression, and administering a 5HT<sub>1A</sub> receptor antagonist to rats given MDMA reduced adjacent lying, a prosocial behavior (Morley et al. 2005). This occurs likely through an increase in oxytocin associated with stimulating 5HT<sub>1A</sub> receptors (Thompson et al. 2007). Pre-administration of the 5HT<sub>1A</sub> and  $\beta$  adrenergic antagonist pindolol had few effects in a sample of men, but the researchers did not assess

interpersonal closeness or social interactions (Hasler et al. 2008). A naturalistic study comparing blood oxytocin in people with and without detectable blood MDMA found that MDMA was associated with elevated oxytocin (Wolff et al. 2006), a hormone that may increase trust and accuracy of emotion perception as well as regulating water/sodium balance (Domes et al. 2007; Zak et al. 2005). Other indirect effects of serotonin release include elevation in cortisol (Grob et al. 1996; Harris et al. 2002; Mas et al. 1999), a hormone with a complex and sometimes paradoxical relationship to stress and challenge (Het and Wolf 2007; Putman et al. 2007; Wirth and Schultheiss 2006). Dopamine release likely plays a role in elevating positive mood and euphoria, which may partially contribute to an enhanced sense of confidence when facing emotionally intense feelings or memories. Administering the D<sub>2</sub> antagonist haloperidol decreased positive mood and increased anxiety after MDMA, suggesting that indirect stimulation of D<sub>2</sub> receptors may play a role in some MDMA effects on mood (Liechti and Vollenweider 2000a). There are no studies to date investigating the role played by norepinephrine release on the cardinal effects of MDMA.

Though they differ in some respects, early and later pharmacological profiles of MDMA reported an affinity for specific serotonergic, noradrenergic, cholinergic and histaminergic receptors (see Table 3 below). It is possible but not yet demonstrated that 5HT<sub>2B</sub> and  $\alpha_2$  receptors may contribute to at least some of the subjective effects of MDMA, while little is known as to whether there are any potential contributions from M<sub>3</sub> or H<sub>1</sub> receptors. 5HT<sub>2B</sub> receptors in the medial amygdala may contribute to the anxiolytic effects of MDMA, as may also be true for the serotonin releaser and 5HT<sub>2B</sub> agonist fenfluramine. Direct MDMA stimulation of postsynaptic  $\alpha_2$  adrenoceptors may also help individuals remain emotionally calm despite noradrenergic activation, as with related  $\alpha_2$  agonists clonidine and guanfacine, possibly through altering the balance between  $\alpha_1$  to  $\alpha_2$  stimulation (Franowicz and Arnsten 1998).

**Table 4** Receptor binding profiles for MDMA recorded from the NIMH Psychoactive Drug Screening Program Database (PDSP)

Receptor	Ki (mcM)	Hot Ligand	Species	Source	Reference
Serotonin transporter	0.072 or 0.102	Functional (1), 3H-citalopram (2)	Rat, Human	Brain, Cloned	(Jones et al. 2004; Setola et al. 2003)
Norepinephrine Transporter	0.110	Functional	Rat	Brain	(Setola et al. 2003)
Dopamine transporter	0.278	Functional	Rat	Caudate	(Setola et al. 2003)
5HT <sub>2B</sub>	0.5 or 0.7	3H-LSD	Human	Cloned	(Setola et al. 2003), (PDSP 2007)
$\alpha_{2C}$	1.12	3H-Clonidine	Human	Cloned	(PDSP 2007)
Calcium Channel	1.2	3H-Nitrendipine	Rat	Heart	(PDSP 2007)
$\alpha_{2B}$	1.8	3H-Clonidine	Human	Cloned	(PDSP 2007)
M <sub>3</sub>	1.8	3H-QNB	Human	Cloned	(PDSP 2007)
H <sub>1</sub>	2.1	3H-Pyrilamine	Human	Cloned	(PDSP 2007)
$\alpha_{2A}$	2.5	3H-Clonidine	Human	Cloned	(PDSP 2007)
M <sub>5</sub>	6.3	3H-QNB	Human	Cloned	(PDSP 2007)
M <sub>4</sub>	8.2	3H-QNB	Human	Cloned	(PDSP 2007)
5HT <sub>2A</sub>	8.3	3H-ketanserin	Rat	Cortex	(Lyon et al. 1986)

## Primary Pharmacodynamics

### *Drug Activity Related to Proposed Action*

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection (Greer and Tolbert 1986; Grinspoon and Bakalar 1986). Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion (Cami et al. 2000b; Harris et al. 2002; Hernandez-Lopez et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003; Tancer and Johanson 2001; Vollenweider et al. 1998). Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with ecstasy (see for example Cami et al. 2000 versus Vollenweider et al. 1998). An increase in positive mood, increased access to emotionally intense material, increased interpersonal trust and compassion for the self and others, and anxiolysis likely all contribute to the therapeutic effects of MDMA. It is significant that anxiety is reduced without the physiological effects of a depressant, and that people can still experience and reflect upon intense emotions. Increased interpersonal closeness may permit people to explore usually upsetting thoughts, memories or feelings, and facilitated recall and changes in the meaning of perception may contribute to generating new perspectives about past or current thoughts, feelings and experiences.

To date, no work has specifically addressed the relationship between the pharmacological effects of MDMA and one or more of its proposed therapeutic effects within a psychotherapeutic context. Since pre-treatment with an SSRI significantly attenuates most subjective and physiological effects of MDMA, it is likely that serotonin release contributes to therapeutic effects, such as reduced anxiety and increased positive mood. However, none of the studies employing SSRI pre-treatment occurred in a therapeutic setting, and none of these studies assessed interpersonal closeness or social interaction. Serotonin release could contribute to proposed therapeutic effects via indirect activation of serotonin receptors, or its therapeutic effects may arise because serotonin influences levels of neuroendocrine hormones, such as oxytocin or arginine vasopressin. Since pre-treatment with the dopamine D<sub>2</sub> receptor antagonist haloperidol reduced positive mood and increased anxiety after MDMA (Liechti and Vollenweider 2000a), indirect effects of dopamine release also appear to play a role in one potentially therapeutic effect. However, preventing action at D<sub>2</sub> receptors had less impact on either subjective or physiological effects of MDMA when compared with serotonin release (Liechti et al. 2000a). While research reported that pre-treatment with the 5HT<sub>2A</sub> antagonist ketanserin attenuated perceptual alterations after MDMA (Liechti et al. 2000b), researchers did not employ a measure that would have allowed them to determine whether 5HT<sub>2A</sub> receptor activation played a role in potentially therapeutic effects, as facilitated recall or changed meaning of perception.

### **Secondary Pharmacology**



### *Safety Pharmacology*

The psychotherapeutic effects of MDMA are accompanied by dose-dependent physiological effects including vasoconstriction and increased heart rate and blood pressure (see pp. 44-48 Baggott et al. 2001; Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2003). Physiological effects of MDMA reach their maximum within 1 and 2 hrs after oral MDMA administration and subside within 6 hrs of drug administration (Harris et al. 2002; Vollenweider et al. 1998; Liechti et al. 2001; see also Baggott et al. 2001). Data on maximum changes in heart rate and blood pressure collected from human studies published or in preparation in mid-2001 are summarized in Table 3.1 in Baggott et al. 2001. Data from more recent reports (Farre et al. 2004; Lamers et al. 2003; Tancer and Johanson 2003) are similar to data from previous reports. Two of three studies found reported that pre-treatment with a selective serotonin uptake inhibitor (SSRI) attenuated elevation in blood pressure and heart rate (Farre et al. 2007; Liechti and Vollenweider 2000b), while the third reported that SSRI pre-administration only attenuated increased heart rate after MDMA (Tancer and Johanson 2007). The 5HT<sub>2A</sub> receptor antagonist ketanserin reduced elevated diastolic pressure (Liechti et al. 2000b), while the D<sub>2</sub> antagonist haloperidol failed to attenuate any of the cardiovascular effects of MDMA (Liechti and Vollenweider 2000a). These findings suggest that cardiovascular effects are at least partially due to serotonergic activity. When given in controlled settings, MDMA produced only slight increases in body temperature (Harris et al. 2002; Liechti et al. 2000b; Tancer and Johanson 2003), with the increase undetected in a number of studies (de la Torre et al. 2000c; Fantegrossi et al. 2004; Farre et al. 2004; Johanson et al. 2006; Liechti et al. 2000a). Humans, unlike rodents, exhibit the same slight elevation in body temperature whether in a warm or a cool environment (Freedman et al. 2005).

The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 2.5 h is expected to produce significant increases in blood pressure and heart rate, but is not expected to produce sustained increases in heart rate or blood pressure above 170/100 mm Hg. The physiological effects of a second dose of MDMA that is half the original dose and given one and a half to two and a half hours after the first dose are not yet known, but personal communication from Michael Mithoefer, the principal investigator conducting the study of MDMA-assisted psychotherapy in people with PTSD, reports that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose (Mithoefer 2007; email sent to L. Jerome on July 7, 2007). A dose of 150 mg may produce peak elevations greater than 170/100, as reported in one participant in the study of Peter Oehen, but these effects were transient (Oehen 2008b).

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocorticotrophic hormone, and dehydroepiandrosterone (DHEA) concentrations (Grob 2001; Grob et al. 1996; Mas et al. 1999), while growth hormone is unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. A second dose of 100 mg MDMA given four hours after an initial dose of 100 mg produced a second increase in cortisol during an interval when cortisol levels were declining (Pacifci et al. 2001b). Harris and colleagues failed to

detect any changes in luteinizing hormone (LH), estradiol, progesterone or follicle stimulating hormone (FSH) in women participants. 40 mg MDMA acutely increased circulating levels of antidiuretic hormone (arginine vasopressin) in eight male volunteers, with maximum levels reached between one and two hours after drug administration (Henry et al. 1998). A naturalistic study reported an association between detectable blood MDMA and elevation in oxytocin (Wolff et al. 2006). Increased retention of fluid is unlikely to be of any consequences in a clinical setting.

Studies conducted in Spain suggest that MDMA acutely affects the immune system (Pacifci et al. 2000; Pacifci et al. 2001a; Pacifci et al. 1999a). These acute changes in immunologic function include reduced CD4 T-cell count, increased NK cell count, and decreased phytohaemoagglutinin A-induced lymphocyte proliferation. These effects are transient and unlikely to last any longer than 24 to 48 hours after drug administration. MDMA decreased levels of the immune system stimulating and proinflammatory cytokine interleukin 2 (IL-2) and increased levels of the immunosuppressive and anti-inflammatory cytokine interleukin 10 (IL-10) (Pacifci et al. 2004; Pacifci et al. 2001). Generally, MDMA appears to decrease the concentration of Th1 cytokines and increase Th2 cytokines measured in blood. For example, the CD4 T-cell count decrease was similar in magnitude to that produced by 0.8 g/kg oral ethanol (the equivalent of 4-5 drinks) in the same report (Pacifci et al. 2001b). The mechanism of immunomodulation is unclear but may be at least partly due to increased glucocorticoid levels or sympathomimetic activity, and activity at  $\alpha$  adrenergic receptors (Connor et al. 2005). Serotonin release probably plays a role in these changes, since paroxetine pretreatment attenuated and in some cases eliminated immunological effects of MDMA (Pacifci et al. 2004) while only partially reducing elevated cortisol. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 2000a; Connor et al. 2000b; Connor et al. 1998).

MDMA acutely affects attention, information processing and memory. MDMA enhances pre-pulse inhibition, the ability of a less intense stimulus (as noise) to reduce startle response to an intense stimulus. MDMA acutely impaired verbal memory and recall for object location without affecting recall of scene change (Kuypers and Ramaekers 2005). MDMA did not affect Stroop task performance, but impaired performance on the Digit Substitution task (Cami et al. 2000a; Gamma et al. 2000). When examined in the context of skills related to driving motor vehicles, MDMA reduced weaving and produced overly cautious response to the actions of another driver (Kuypers et al. 2006; Ramaekers et al. 2006). The mechanism or mechanisms behind these acute changes remains unknown. However, since the noradrenergic and dopaminergic agonist methylphenidate failed to alter verbal memory or driving skills in the same way as MDMA, it is likely that serotonin release contributes directly or indirectly to these effects. Acute effects of MDMA upon verbal and visual memory were no longer apparent 24 hours later.

Published animal and *in vitro* studies have specifically investigated the possibility of hyperthermia, hepatotoxicity and neurotoxicity after MDMA exposure. These types of toxicity appear to be dose-dependent and all available evidence indicates that the risks in

these areas are minimal in the currently proposed study. These areas of toxicity are discussed below.

MDMA may cause modest changes in cerebral blood flow lasting several weeks after drug exposure. These changes have been hypothesized to be the result of short-term down-regulation of serotonergic receptors controlling cerebral vasodilatation (Reneman et al. 2002; Reneman et al. 2000). MDMA induced decreased regional and global cerebral blood flow (CBF) 10 to 21 days after administration (Chang et al. 2000), as reported in a study of 10 ecstasy users given two separate ascending doses of MDMA at a two-week interval, with comparisons made at baseline and after the administration of both doses. Doses per administration in this study ranged from approximately 17 mg (0.25 mg/kg) to approximately 175 mg (2.5 mg/kg). The authors did not find differences in regional or global CBF when 21 MDMA-experienced volunteers (with a reported  $211 \pm 340$  exposures) were compared to 21 nonusers, suggesting that effects on CBF do not last indefinitely, a prospective study in people before and after using ecstasy found changes in rCBF only in one brain area, the dorsolateral prefrontal cortex. There are no known consequences of these changes and neurocognitive performance was not altered in these volunteers.

### Hyperthermia

As discussed above, MDMA administered in a controlled setting produces only a slight increase in body temperature, and ambient temperature does not enhance or attenuate this slight elevation in humans. However, hyperthermia is one of the most commonly reported serious adverse events in ecstasy users (Baggott et al. 2001; Henry and Rella 2001). Researchers working with rodent models have suggested several potential causes, including nonshivering heat production or the action at norepinephrine receptors, and they have reported that hyperthermia is more likely in group-housed rodents (Fantegrossi et al. 2003; Mills et al. 2004; Sprague et al. 2004a; Sprague et al. 2004b). However, given that rodents face different thermoregulatory challenges when compared to humans (Gordon 2007) and given that human body temperature after MDMA is unaffected by ambient temperature, it is not clear whether and to what degree these models are relevant to humans. Hyperthermia may be dose dependent, as suggested by case series of people who took ecstasy in the same London area nightclub on the same evening (Greene et al. 2003). Hence it is possible that a dose of 150 mg may produce a greater elevation in body temperature than a dose of 125 mg. A case report and at least some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans (Martin et al. 2007; Sprague et al. 2007). However, even when given in a warm environment, 2 mg/kg MDMA did not produce a clinically significant increase in body temperature (BT) (Freedman et al. 2005). In addition, the investigator in Switzerland who has administered 150 mg to one participant on two occasions reported variations in BT in the same subject across sessions involving 125 and 150 mg (Oehen 2008a, personal communication). To date, there have been no cases of clinically significant hyperthermia in any human MDMA trial, and it is unlikely to occur in this study.

### Psychiatric Problems

Psychiatric problems occurred in 22.1% of 199 case reports examined in 2001. Psychiatric symptoms included affective responses, as dysphoria, anxiety or panic, and psychotic response, as well as cases with mixed psychotic and affective features (Baggott et al. 2001). The most common problem reported as psychotic response (see for example McGuire et al. 1994). There was a family history of psychiatric disorders in a large minority of cases of psychosis after MDMA. These psychiatric problems generally occurred in experienced rather than novice ecstasy users. Some panic responses resolved without further assistance (Whitaker-Azmitia and Aronson 1989). The mechanisms behind ecstasy-associated psychiatric problems remain unclear but are likely the result of an interaction between pharmacology and individuals susceptibility. The difficulty of assessing the frequency of these events is increased given that that pre-existing psychiatric problems occur in people who go on to use ecstasy (Huizink et al. 2006) and findings of an association between use of ecstasy and other drugs and self-reported symptoms of anxiety and depression. As described earlier, most cases of psychological distress after ecstasy use resolved after supportive care ((Liechti et al. 2005; Williams et al. 1998). Anxiety responses reported in controlled trials has never required clinical intervention and abated with the waning of drug effects.

#### Hepatotoxicity

Liver damage was reported in approximately 16% of 199 case reports examined in an initial review of the literature (Baggott et al. 2001), making hepatotoxicity the third most common serious adverse event occurring in ecstasy users. There is more than one pattern of ecstasy-related hepatotoxicity. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet (Dykhuisen et al. 1995; Ellis et al. 1996; Ellis 1992). In other cases, hepatotoxicity has occurred after regular ecstasy use for months (Andreu et al. 1998). Standard toxicity studies failed to find liver damage after MDMA in rats or dogs after 28 days of exposure (Frith et al. 1987), nor have any cases of liver disease arisen during controlled studies. Examining case reports and a number of in vitro studies suggests an association between hyperthermia and hepatotoxicity. However, liver disease also occurred in some individuals without the occurrence of hyperthermia, with it appearing after continued use and resolving after abstinence, suggesting a potential immunological response.

Because hepatotoxicity has been noted in ecstasy users, in vitro and in vivo studies have examined the hepatotoxicity of MDMA. These studies show that high doses of MDMA can impair liver cell viability. In vitro studies found that high to very high concentrations of MDMA increased ALT, AST and LDH activity (Beitia et al. 2000), increased pro-fibrogenic activity in cultured stellate cells (Varela-Rey et al. 1999) and slightly reduced cell viability without producing lipid peroxidation (Carvalho et al. 2001). Incubating cells with slightly smaller concentrations of MDMA at high temperatures further reduced cell viability (Carvalho et al. 2001; Montiel-Duarte et al. 2002), with apoptosis (cell death) seen when concentrations of MDMA approximately eleven times those seen in humans were incubated at high temperatures (Montiel-Duarte et al. 2002). Hepatotoxicity is probably the result of oxidative stress (Carvalho et al. 2004; Montiel-Duarte et al. 2004). Peak liver exposure to MDMA in the proposed clinical study should be approximately

one-eleventh the concentration shown to impair cell viability in these in vitro studies. No cases of liver disease or hepatotoxicity has occurred in a controlled trial of MDMA.

### Hyponatremia

A number of case reports describe hyponatremia after ecstasy use (Baggott et al. 2001; Henry and Rella 2001), with case reports of hyponatremia appearing subsequent to review (see for example Brvar et al. 2004; Rosenson et al. 2006). Behavioral factors, including vigorous exercise and consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones arginine vasopressin and oxytocin likely all contribute to these very rare but serious adverse events in ecstasy users. Hyponatremia has not occurred during a controlled study.

### Neurotoxicity

Extensive studies in animals indicate that high or repeated dose MDMA exposure can damage serotonergic axons originating in the dorsal raphe nucleus of the brainstem (Molliver et al. 1990). This is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter. Although some regrowth occurs, seemingly permanent redistribution of axons was noted in a study with squirrel monkeys (Hatzidimitriou et al. 1999). These serotonergic changes have not been associated with lasting behavioral impairment in the vast majority of animal studies, despite dramatic serotonin depletions. The great volume of research addressing MDMA neurotoxicity has been extensively reviewed and discussed in past and current revisions of the Investigator's Brochure (Baggott et al. 2001; Cole and Sumnall 2003b; Green et al. 2003; Jerome 2004; 2005). Several studies in nonhuman primates suggest that previous research employed doses or regimens exceed doses normally used by humans (Bowyer et al. 2003; Fantegrossi et al. 2004; Mehan et al. 2006). Two studies performed by the same team of researchers comparing MDMA administration in rats (three 7.5 mg/kg doses given i.p.) found changes in some but not other markers of damage to the serotonin system (Wang et al. 2005; Wang et al. 2004), specifically finding a dissociation between changes in serotonin levels and proteins that mark neuronal injury. Considering these findings, it appears that the nature and extent of MDMA neurotoxicity remains contentious.

Findings from nonhuman animal research led researchers to compare ecstasy users with non-user controls. There are several reviews of this literature and discussion of it in the Investigator's Brochure (Baggott et al. 2001; Cole and Sumnall 2003a; Kish 2002; Laws and Kokkalis 2007; Zakzanis et al. 2007). To date, most retrospective studies have detected lower estimated serotonin transporter (SERT) sites in current ecstasy users, elevated numbers of anxiety or depression in current and former ecstasy users, and impaired verbal memory and executive function (decision-making and planning) in ecstasy users. These findings suggest that regular and especially heavy ecstasy use may pose risks of transient changes in SERT site number (Reneman et al. 2001; Reneman et al. 2006b) and long-term effects (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004). These retrospective studies contain a number of methodological flaws, particularly with respect to finding appropriately matched controls (Gouzoulis-Mayfrank and Daumann 2006).

Vollenweider and colleagues recently measured serotonin transporter density using positron emission tomography (PET) with [ $^{11}\text{C}$ ]McN5652 before and after a single dose of MDMA (Vollenweider et al. 2000, data presented at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine). Vollenweider and colleagues were unable to detect any lasting effect of 1.5 or 1.7 mg/kg MDMA in a pilot study with six MDMA-naïve healthy volunteers and in a second study with two additional volunteers. This measurement technique was validated in a study using a baboon exposed to a neurotoxic MDMA regimen (Scheffel et al. 1998), and this validation study found that PET tended to overestimate serotonin transporter changes in most cases. The same team also presented data from a prospective study of MDMA on cognitive function, reporting failure to find impaired cognitive function after MDMA administration (Ludewig S et al. 2003).

More recently, a series of prospective studies examined brain serotonin transporter sites, signs of neuronal injury, brain activity and cognitive function in people before and after their first few uses of ecstasy, ranging from 0.5 to 6 tablets (de Win et al. 2007; Jager et al. 2007b; Schilt et al. 2007). The researchers conducting these studies recruited people who reported an interest in taking ecstasy in the future and assessed them when first contacted and again shortly after they reported their first few uses of ecstasy. These findings, described in more detail above in “Risks” and in pp. 3-4 of the current revision of the Investigator’s Brochure suggest that low ecstasy use has little impact on brain structure or function. Taken together, MDMA may be neurotoxic in high or repeated doses, but lower or less frequent doses are not neurotoxic, with little to no indications of long-term effects after moderate use.

#### Developmental Toxicity

There remains a paucity of findings concerning developmental or reproductive toxicity in humans. An early investigation reported detecting increased developmental problems in births from ecstasy-using mothers (McElhatton et al. 1999) while a later investigation examining a specific defect failed to detect an association between ecstasy use and this defect, due in large part to low levels of ecstasy use in the sample (Bateman et al. 2004). Studies in rats have consistently found developmental effects of repeated doses of MDMA, including impairment on learning and memory (Meyer et al. 2004; Vorhees et al. 2004; Williams et al. 2005). It is possible that exposure to MDMA during the third trimester in humans could have similar effects. To date, pregnant women have not been enrolled in any controlled study of MDMA, and there is no plan to include them in the proposed study.

#### *Common side effects*

Common side effects are described in “Risks of MDMA” above and include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common side effects include restlessness, paresthesias (odd somatic feelings, as reporting tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, and nystagmus (eye-wiggle). These effects are transient and wane as drug effects are waning. Sub-acute effects that either continue for the next 24 hours or appear later include insomnia, fatigue, weakness,

heavy legs, dry mouth, low mood or irritability. Fewer people report sub-acute effects when compared with people reporting acute effects. More information on drug side effects is contained on pp. 20-22 of the investigator's brochure.

#### *Acute Adverse Effects*

Approximately 5% of participants enrolled in controlled trials with MDMA have had clinically significant elevations in blood pressure, as described above in "Risks of MDMA," though none have required any clinical interventions and blood pressure returned to normal. While maximum peak blood pressure during a given session in some cases rose above the cut-off of 150 SBP or 110 DBP for making more frequent measures, as with the maximum SBP peak seen in the first stage 2 open-label session (179, n = 6) or the average peak for the second stage 2 open-label session (151, n = 6), or peak DBP during second experimental session of 113 (from amongst both MDMA and placebo sessions, n = 21). None of the maximum peaks in blood pressure ever rose to the point wherein any further treatment was necessary. Likewise, maximum body temperature could rise above normal temperature, as with the maximum peak of 100 F during the first experimental session (n = 23, MDMA and placebo conditions combined), but simply lowering the ambient temperature was sufficient to lower body temperature. As also noted in "Risks of MDMA" above, no drug-related serious adverse effects have occurred, and the majority of ecstasy users visiting emergency departments do so because of anxiety or panic (Liechti et al. 2005; Williams et al. 1998). However, there are case reports of a number of serious adverse events occurring in ecstasy users, including hyperthermia, psychological distress and hepatotoxicity. More information on these events is described above in "Safety Pharmacology" above.

#### *Abuse Liability*

MDMA possesses moderate abuse liability, as discussed above in "Risks to Participants" and below in "Additional Information."

#### **Pharmacokinetics/Toxicokinetics**

The pharmacokinetics of MDMA, summarized in Table 4, have been primarily characterized by a group of Spanish researchers in samples of male subjects, with the exception of one publication from a team of researchers in the Netherlands that was not primarily concerned with pharmacokinetics. Additional pharmacokinetic parameters for MDMA and metabolites are given in the papers cited in Table 4. For example, after 125 mg MDMA, total clearance for MDMA was  $51.1 \pm 14.1$  per hr, while renal clearance was  $13.0 \pm 5.4$  per hr (de la Torre et al. 2000a). The findings of the Spanish researchers are consistent with other investigations using limited doses (Fallon et al. 1999; Hensley and Cody 1999) or illicit users (Crifasi and Long 1996; Moore et al. 1996; Ramcharan et al. 1998). More recently, a team of researchers in Maryland replicated this work in an ethnically varied sample of men and women using doses of 1 and 1.6 mg/kg MDMA (Kolbrich et al. 2008). They report findings similar to those of de la Torre and colleagues, but also report finding inter-subject variability and gender differences in MDMA metabolism, with women having higher peak values for MDMA and the minor metabolite MDA and lower values for major metabolite HMMA than men. The

significance of these differences are unclear, and this is the first detailed study of MDMA pharmacokinetics in men and women.

As can be seen in Table 5, MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). These dose-dependent kinetics appear to be due to dose-dependent metabolism rather than changes in absorption or excretion. Mas et al. (1999) reported that 75 mg and 125 mg doses of MDMA had similar absorption constants and absorption half-lives. On the other hand, non-renal clearance for 125 mg MDMA was approximately half that of 75 mg MDMA. The dose-dependent metabolism of MDMA is at least partially due to inhibition of CYP2D6, as discussed below. It has also been established that the fraction of MDMA bound to dog plasma proteins is approximately 0.4 and is concentration-independent over a wide range of concentrations (Garrett et al. 1991). Therefore, changes in plasma partitioning are not likely to be significant.



**Table 5.** MDMA Pharmacokinetics

<b>MDMA Dose</b>	<b>N</b>	<b>C<sub>max</sub></b> <i>μg/l</i>	<b>T<sub>max</sub></b> <i>H</i>	<b>AUC<sub>0-24</sub></b> <i>μg*h/l</i>	<b>AUC/dose</b> <i>μg*h/(l*mg)</i>	<b>Reference</b>
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8.6	Mas et al. 1999
75	1 2	178 (no SD)	3	Not reported	NA	Lamers et al. 2003
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	24.31 ± 7.7	(de la Torre et al. 2000c)
100	9	180 ± 33	2 ± 0.26	1452 ± 771	14.52 ± 7.7	Farre et al. 2004
100	7	208.7 ± 17.1	16 ± 0.4	Not reported	NA	(Pizarro et al. 2004)
100	7	232.9 ± 45.3	1.5	Not reported	NA	Segura et al. 2005
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	(de la Torre et al. 2000a)

<b>MDMA Dose</b>	<b>N</b>	<b>k<sub>a</sub></b> <i>/h</i>	<b>k<sub>e</sub></b> <i>/h</i>	<b>T<sub>1/2</sub></b> <i>H</i>	<b>MDA T<sub>1/2a</sub></b> <i>H</i>	<b>Reference</b>
50	2	Na	na	2.7 and 5.1	Na	(de la Torre et al. 2000c)
75	8	2.3835 ± 2.1362	0.1171 ± 0.0818	7.86 ± 3.58	0.42 ± 0.2	Mas et al. 1999
100	8	2.7 ± 1.53	0.081 ± 0.018	8.96 ± 2.27	1.31 ± 0.55	(de la Torre et al. 2000c)
100	7	na	0.07 ± 0.03	11.8 ± 4.4	na	Pizarro et al. 2004
125	8	2.1253 ± 1.1001	0.0923 ± 0.0428	8.73 ± 3.29	0.41 ± 0.22	Mas et al. 1999
150	2	Na	na	6.9 and 7.2	Na	(de la Torre et al. 2000a)

Farre and colleagues reported the pharmacokinetics of a second dose of 100 mg MDMA given 24 hours after an initial 100 mg dose in nine men (Farre et al. 2004). C<sub>max</sub> was 232. ± 39 μ/L, AUC<sub>(24-48)</sub> was 2564 ± 762 μg/\*h/L, T<sub>max(24-48)</sub> was 25.5 ± 0.33 h, and AUC/dose was 25.64 ± 7.6 μg/\*h/l\*mg. Maximal MDMA concentration after the second dose was similar to maximal concentration after the slightly higher dose of 125 mg (see Table 4 above), probably as a result of non-linear pharmacokinetics. De la Torre was first to report evidence of non-linear pharmacokinetics, and a recent report supports these findings (de la Torre et al. 2000a; Kolbrich et al. 2008). Based on these findings, metabolism of an initial dose will also be affected by a supplemental dose. However, since the size and timing of this dose are different from the dosing regimen employed by Farre and colleagues, it is not clear whether the supplemental dose will produce slightly

higher maximal values than expected after the supplemental dose only or the combined dose, or whether it will instead lengthen  $T_{max}$ .

*Summary of Pharmacokinetic Parameters :*

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called  $\alpha$ -methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, 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; Pizarro et al. 2002; Segura et al. 2001). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published (de la Torre et al. 2000a; Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002)(de la Torre et al. 2000; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004). HMMA appears to be the main metabolite in humans (Pizarro et al. 2004). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

Although a number of researchers hypothesized that genetic variations in CYP2D6 activity might influence risk of MDMA toxicity, an examination of the research does not support this concern. Several *in vitro* studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforge et al. 1999; Wu et al. 1997). Compelling *in vivo* evidence of enzyme inhibition was provided by de la Torre et al. (de la Torre et al. 2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant.

Relatively recent reports in humans found no evidence that having a CYP2D6 “poor metabolizer” genotype is by itself a major risk factor for acute MDMA toxicity (de la Torre et al. 2004). At least one poor metabolizer has received MDMA as a participant in a study conducted by the Spanish team (de la Torre et al. 2005) (Segura et al. 2005) without any adverse events occurring. The individual had 60% greater MDMA AUC after a first and a second dose, but the only other reported difference for this participant was a statistically significant increase in amount of NK cells. A comparison of MDMA metabolism in poor and extensive metabolizers found that reduced CYP2D6 function was associated with higher MDMA AUC after the first of two doses of MDMA, but similar levels of MDMA and metabolites after the second dose (de la Torre et al. 2005). The same lack of effects was originally reported in a participant given the similar compound methylenedioxyethylamphetamine, or MDE (Kreth et al. 2000).

Two teams of researchers have investigated the enzymes involved in the formation of MDA from MDMA in human liver microsomes (Kreth et al. 2000; Maurer et al. 2000). Maurer et al. reported that formation of MDA was predominantly catalyzed by CYP1A2 (and to a lesser extent by CYP2D6), but did not present detailed results of their

experiments. In a publication focusing on MDE metabolism, Kreth and colleagues reported high correlations between MDMA and MDE N-dealkylation and MDE N-dealkylation and human liver microsome CYP2B6 content. MDE N-dealkylation and CYP1A2 levels were also significantly correlated. This indicates that CYP2B6 and CYP1A2 participate in the formation of MDA. The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989).

MDMA is a chiral compound, meaning it comes in two forms or enantiomers. However, all investigations in humans and most in nonhuman animals have almost exclusively administered the racemate (a mixture of both enantiomers). Studies in human volunteers (Fallon et al. 1999; Hensley and Cody 1999) and rodents (Cho et al. 1990; Fitzgerald et al. 1990; Matsushima et al. 1998) indicate that the disposition of MDMA is stereoselective, with the S-(+)-enantiomer having a shorter elimination half-life and greater excretion than the R-(-)-enantiomer. For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (Crifasi and Long 1996; Ramcharan et al. 1998). The stereoselective pharmacokinetics of MDMA is reflected in formation of MDA and DHMA enantiomers (Fallon et al. 1999; Pizarro et al. 2004; Pizarro et al. 2003). In the first 24 hours after MDMA administration, greater plasma and urine concentrations of S-(+)-MDA than its R-enantiomer occur (Fallon et al. 1999; Moore et al. 1996). By contrast, R/S ratios of HMMA are more similar to those for MDA (greater amounts of R-(-)-HMMA than S-(+)-HMMA during the first 24 hours), or there is no findings of a difference between concentrations of the two enantiomers of HMMA (Pizarro et al. 2004; Pizarro et al. 2003).

#### *Absorption, Distribution, Metabolism, Excretion*

The oxidation of the methylenedioxy group can take place via enzymes such as cytochrome p450 (Hiramatsu et al. 1990; Kumagai et al. 1991; Lim and Foltz 1988; Tucker et al. 1994) or by a non-enzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit (Kumagai et al. 1991), rat (Gollamudi et al. 1989; Hiramatsu and Cho 1990; Hiramatsu et al. 1990; Hiratsuka et al. 1995) and human (Kreth et al. 2000; Lin et al. 1997; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low Km component for demethylenation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylenation, including CYP1A2 and CYP3A4.

**Table 6.** Urinary Recovery for MDMA and Metabolites (de la Torre et al. 2000a)

MDMA Dose mg (mol)	N	Urinary Recovery (mol)				Dose Excreted (%)
		MDMA	MDA	HMMA	HMA	
50 (259)	2	20.7 and 40.9	1.4 and 1.0	152.0 and 89.2	4.7 and 4.2	69.1 and 38.3
75 (358)	8	71.2 ± 13.7	3.5 ± 0.9	128.3 ± 21.8	5.4 ± 0.4	53.7 ± 11.4
100 (518)	2	232.6 and 74.7	1.4 and 5.6	59.8 and 124.0	2.9 and 6.8	57.3 and 40.7
125 (647)	8	169.6 ± 69.5	6.4 ± 2.7	148.3 ± 102.8	6.2 ± 3.7	51.0 ± 16.2
150 (776)	2	160.3 and 333.3	2.6 and 4.7	122.2 and 82.4	4.1 and 3.7	37.3 and 54.7

The urinary excretion of MDMA and its metabolites was first characterized by de la Torre and colleagues, with data from that study presented in Table 5 above. 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; Segura et al. 2005; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA reported after administration of 100 mg MDMA to four men are  $91.8 \pm 23.8$  mol and 17.7% recovery (Segura et al. 2001). 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).

### Toxicology

The toxicity of MDMA has been investigated in numerous animal and *in vitro* studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Finally, 28-day toxicity studies in canines and rodents have been performed (Frith et al. 1987), and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

#### *Acute toxicity*

Acute toxicity is described above in “Safety Pharmacology”, including both common side effects and effects occurring in ecstasy users. The estimated LD<sub>50</sub> for MDMA in humans is between 10 and 20 mg/kg (Frith et al. 1987; Hardman et al. 1973). To date, most controlled studies rarely administered doses above 2 mg/kg. The proposed doses of 150 followed by 75 mg (cumulative dose of 225 mg) or approximately 2.1 mg/kg followed by approximately 1 mg/kg (cumulative dose of 3.21 mg/kg) is below the estimated LD<sub>50</sub> in humans.

#### *Reproductive Toxicity*

Investigations of the reproductive and developmental toxicity of MDMA are described in “Safety Pharmacology” above. These studies include inconclusive findings in humans and findings in rodents suggestive of a critical period during which exposure to MDMA

may impair learning or memory. Pregnant women will not be enrolled in this training program.

### **Previous Human Experience**

Several accounts describe the use of MDMA as an adjunct to psychotherapy prior to its placement in schedule 1 (Adamson 1985; Stolaroff 2004), and between 1988 and 1993 in Switzerland (Gasser 1994; Widmer 1998). This therapy did not occur in the context of a controlled clinical trial. MDMA may have been given to thousands of individuals during these time periods without any fatalities or serious adverse events (Gasser 1994; Holland 2001; Rosenbaum and Doblin 1991). Psychotherapists used MDMA-assisted psychotherapy in the treatment of moderate psychological difficulties (“neuroses”), relationship difficulties, posttraumatic stress disorder, and anxiety in response to diagnosis with a potentially fatal illness. Therapists described relying on a mixture of therapeutic techniques that included confronting and working with the experience as it occurred and speaking openly with others during the experience.

In the 1980s, two researchers independently published an uncontrolled clinical trial and an uncontrolled investigation into MDMA-assisted psychotherapy (Downing 1986; Greer and Tolbert 1986). The psychotherapy that Greer and Tolbert conducted took place in a setting similar to that used for psychedelic-assisted psychotherapy, including focusing on inner experience. Greer and Tolbert used doses between 75 and 150 mg MDMA, sometimes with supplemental doses administered later (Greer and Tolbert 1986). Participants in the uncontrolled study of MDMA-assisted psychotherapy reported changes in attitudes and benefits afterwards.

The first controlled investigation of MDMA took place almost a decade after the uncontrolled studies (Grob et al. 1996), followed two years later by another controlled trial (Vollenweider et al. 1998). Starting in the mid to late 1990s, at least seven research teams in Europe and the US began conducting and publishing clinical MDMA research using healthy volunteers, and two recent reviews summarized findings from many of these studies (Baylen and Rosenberg 2006; Dumont and Verkes 2006). Since then, a second team of researchers in the Netherlands and a team based in Maryland published their first findings from human MDMA studies (Dumont et al. 2008; Kolbrich et al. 2008). Findings from controlled human studies of MDMA are also discussed in detail in the investigator’s brochure (Baggott et al. 2001; Jerome 2004; 2005; 2007; Jerome and Baggott 2003), and they are addressed earlier in this section. The first studies assessed physiological, subjective, psychological and neuroendocrine effects, and reported that MDMA possessed a unique pharmacological profile. Some of these first studies examined brain activity (Frei et al. 2001; Gamma et al. 2000) cardiac function (Lester et al. 2000), and effects of MDMA on attention and information processing (Cami et al. 2000b; Gamma et al. 2000).

To date, MDMA has been administered to approximately 390 research participants, without any occurrences of drug-related serious adverse events. Human MDMA studies have continued to investigate the subjective and physiological effects of MDMA, and its metabolism and detectability in several body fluids. In published reports, investigators

administered doses ranging from approximately 35 mg (0.5 mg/kg) to 145 to 150 mg (2 mg/kg) (Freedman et al. 2005; Harris et al. 2002; Lester et al. 2000) (Kolbrich et al. 2008), and in an unpublished report, researchers administered 0.25 and 2.5 mg/kg MDMA as well (Grob 2001). The average dose examined in human MDMA studies is between 1 and 2 mg/kg. Studies of the physiological effects of MDMA include investigations of immunological effects (as Pacifici et al. 2004; Pacifici et al. 1999b; Pacifici et al. 2002; Pacifici et al. 2001b), neuroendocrine effects (Forsling et al. 2001; Grob et al. 1996; Harris et al. 2002; Liechti and Vollenweider 2001), cardiovascular and cardiac effects (Lester et al. 2000; Mas et al. 1999) and body temperature (Freedman et al. 2005), and employed brain imaging and quantitative electroencephalography (Frei et al. 2001; Gamma et al. 2000). Researchers have studied self-reported subjective and reinforcing effects (Cami et al. 2000b; Dumont et al. 2008; Grob et al. 1996; Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003) and observed effects (Harris et al. 2002), and they have studied such specific effects as enhancement of pre-pulse inhibition (Vollenweider et al. 1999), performance on attentional and information processing tasks such as the continuous performance, Stroop and digit symbol tasks (Cami et al. 2000b; Dumont et al. 2008; Gamma et al. 2000), cognitive skills related to driving motor vehicles (Kuypers and Ramaekers 2005; 2007; Kuypers et al. 2006; Ramaekers and Kuypers 2006; Ramaekers et al. 2006), including specific effects of nocturnal dosing (Kuypers et al. 2007), and similarity to a stimulant versus a serotonergic drug (Johanson et al. 2006). As described above, researchers have also examined the role of serotonin release, 5HT<sub>2A</sub> and D<sub>2</sub> receptors in producing MDMA effects and MDMA pharmacokinetics (de la Torre et al. 2004; Farre et al. 2007; Liechti and Vollenweider 2001; Tancer and Johanson 2007).

A team of researchers in the US are about to complete their research study of MDMA-assisted psychotherapy in people with PTSD, while researchers in Switzerland are engaged in an ongoing study of MDMA-assisted psychotherapy (Mithoefer 2007a; b; 2008; Oehen 2006) and researchers in Israel are conducting a study of MDMA-assisted psychotherapy in people with PTSD (Mojeiko 2006). After undergoing introductory and preparatory psychotherapy, study participants in these studies receive two to three day-long sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Participants receive integrative psychotherapy on the day after each session and often on a weekly basis in between and after each MDMA-assisted session. These studies employ an initial dose of 125 mg MDMA followed 2 to 2.5 hours later by a supplemental dose of 62.5 mg MDMA. One of the two ongoing studies has enrolled all study participants, and preliminary results appear promising (Mithoefer 2007b). The other study has enrolled half of the 12 subjects planned for this study. Another study will soon be recruiting people with advanced-stage cancer to examine MDMA-assisted psychotherapy as a means of reducing anxiety arising from the cancer diagnosis (Halpern 2006). To date, the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored three of four studies, with the fourth sponsored by the principal investigator and private benefactors.

Previous experience with MDMA indicates that it can be safely administered to humans within a research or therapeutic setting, and preliminary examination of data from a study of MDMA-assisted psychotherapy in people with PTSD suggests that MDMA improves

PTSD symptoms when used as a psychotherapeutic adjunct. The independent rater conducted a preliminary analysis of CAPS scores at baseline and two months later detected a significant condition effect ( $p < 0.05$ ). Average baseline scores for people in both conditions were comparable (79.6 for MDMA condition and 78.4 for placebo), but two months after the second experimental session, the average CAPS score for people in the MDMA condition was 27.6, while the average CAPS for people in placebo was 59.1. Eight of 13 participants no longer met criteria for PTSD two months after the second experimental session while only two of eight placebo participants no longer met criteria for PTSD diagnosis. Furthermore, a comparison of baseline assessment of neurocognitive function and assessment two months after the second experimental session did not find any significant differences in either MDMA or placebo participants (Wagner 2008, personal communication). The data examined in this analysis has not yet been subjected to quality assurance and data from one participant remains to be added, but there were few outliers in the data and it is unlikely that additional data will change results.

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## **Additional Information**

### **Facilities**

Introductory, MDMA-assisted and integrative psychotherapy will take place in the offices of Ingrid Pacey MB. BC, in Vancouver BC. The offices consist of a set of three rooms, including a private bathroom and kitchen and include a refrigerator and microwave. The main room is comfortably furnished and private. There is artwork on the walls, and stained glass in some windows. Subjects may sit or lie on a couch. The offices are furnished with beds that allow for two people to remain overnight. The offices are lower than ground level. They can be heated, and fans are used for cooling. The offices have an enclosed courtyard. The office will contain equipment for assessing blood pressure, pulse, and body temperature and an automatic external defibrillator. The offices are not within a hospital, but the location is a five minute drive from two hospitals with emergency departments, the University of British Columbia Hospital and St. Paul's hospital. One therapist can reach the offices within five to ten minutes of contact if necessary.

### **Abuse Liability**

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.

## Appendix A: Visit by Visit Description

Participants who consent to take part in the study will undergo the following sequence of events:

- *Randomized sessions*
- **Screening/Evaluation (Visit 3)**: A two to three hour long medical and psychiatric evaluation. A physician working with the investigators will perform medical history and physical examination and ECG. The independent assessor will diagnose psychiatric disorders with the SCID. The physician or principal investigator will draw blood for laboratory tests. The independent rater will administer the CAPS and the participant will complete the BDI. The independent rater will administer the RBANS and PASAT. If a participant meets study eligibility criteria after evaluation, he or she will be scheduled for an introductory psychotherapy session. The independent assessor will re-evaluate any participant who undergoes the screening and baseline evaluation prior to discontinuing psychiatric medication. During re-evaluation, the independent assessor will administer the CAPS and the participant will complete the PDS and BDI during a visit occurring after an interval of at least five times drug half-life.
- **Introductory Psychotherapy visits (Visits 4-6)**: Three 60 to 90 minute introductory psychotherapy sessions with both psychotherapist investigators. These sessions will help the therapists and participant to learn about each other and discuss the participant's goals, hopes and fears in relation to upcoming MDMA-assisted psychotherapy, and the events and procedures that will occur during MDMA-assisted psychotherapy. Introductory sessions will be recorded to audio and video, and participants will have an opportunity to review the recordings. On the third introductory session, participants will receive instructions and restrictions relating to food and drug consumption for the night before and morning of the MDMA-assisted session. Participants must be randomized to one of the two conditions (active placebo or experimental dose) prior to the first MDMA-assisted psychotherapy session.
- **MDMA-assisted Psychotherapy Session 1 (Visit 7)**: First eight-hour long randomized (active placebo versus experimental dose) MDMA-assisted psychotherapy session. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapists deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of the session recording upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant during the experimental session or at some time after it has ended. The significant other can remain overnight with the participant but does not have to do so. All participants will remain at the offices of Dr. Pacey overnight. A same-sex attendant versed in caring for people

- undergoing difficult psychological experiences will remain with the participant during the overnight stay.
- **Integrative Psychotherapy On the Day After Experimental Session (Visit 8):** A ninety-minute long psychotherapy session with both psychotherapist-investigators always occurring on the morning of the day after MDMA-assisted psychotherapy. The participant will discuss his or her thoughts, feelings, memories or experiences that occurred during the experimental session and the participant and investigators will seek to integrate this material into everyday life. The session will be recorded to audio and video and participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy.
  - **Integrative Psychotherapy Sessions Between Experimental MDMA-assisted Session 1 and 2 (Visit 9-10, 10.x):** Two or more sixty to ninety minute psychotherapy sessions with both psychotherapist-investigators during which they and the participant continue to integrate material from MDMA-assisted psychotherapy sessions. The investigators and participant may schedule additional integrative sessions upon participant request and therapist-investigator mutual agreement. These sessions will be recorded to audio and video and participants may view session recordings upon request.
  - **MDMA-Assisted Psychotherapy Session 2 (Visit 11):** The second eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during the experimental session or after the experimental session is over. All participants will remain at the offices of Dr. Pacey overnight. Significant others may remain overnight with participants but do not have to do so.
  - **Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy 2 (Visit 12):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the second experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy.
  - **Integrative Psychotherapy After MDMA-Assisted Session 2 (Visits 13-14, 14.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators

- occurring after the second MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.
- **MDMA-Assisted Psychotherapy Session 3 (Visit 15):** The third eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during or after the experimental session. All participants will remain at the offices of Dr. Pacey overnight. Significant others may remain overnight with participants but do not have to do so.
  - **Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy 3 (Visit 16):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the third experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy.
  - **Integrative Psychotherapy After MDMA-Assisted Session 3 (Visits 17-18, 18.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators occurring after the third MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.
  - **Evaluation Six weeks After Third MDMA-assisted Session (Visit 19):** A ninety to 120 minute long (1.5-2 hour long) evaluation. The independent assessor will administer the CAPS, RBANS and PASAT, and the participant will complete the BDI and PDS.
  - **Study Blind Broken for Individual Subject (Visit 19):** A 30 to 60 minute long meeting with the therapist-investigators. The participant and both therapists will learn participant condition assignment. The independent rater will remain blind to participant condition assignment. If the individual received active placebo MDMA, then he or she will receive consent materials for the open-label study segment, Stage 2. If a participant received experimental dose MDMA, the participant and investigators will reach a decision as to

whether the participant will enroll in a fourth and optional open-label MDMA-assisted psychotherapy session. If the participant and investigators agree to have a fourth session, then the next review session is scheduled. Any participant who received active placebo and does not consent to take part in Stage 2 will complete the RRPQ. If the investigators believe that an individual assigned to the experimental dose condition might benefit from a fourth and open-label session, then they will discuss an additional session with the participant, who can accept or decline this fourth session.

- *Open-label Sessions for Active Placebo Participants (Stage 2)*
- **Consent for stage 2 (Visit 20):** A 30 to 60 minute meeting with the investigator therapists for participants who learn they received active placebo. They will receive consent materials concerning the open-label study segment. They must give written informed consent to take part in this study segment. Visit 20 may occur on the same day as Visit 19.
- **Stage 2 Baseline Evaluation (Visit 21):** Baseline evaluation for stage 2 (active placebo participants only). CAPS, PDS and BDI scores from the evaluation six weeks after the third experimental session (Visit 19) will serve as baseline scores except in the case where thirty days have passed between those evaluations and the time when the participant entered Stage 2, in which case the independent assessor will perform an additional evaluation, administering the CAPS and BDI prior to entry into Stage 2.
- **Review and Introductory Psychotherapy (Visit 22):** A sixty to ninety minute psychotherapy session with both therapist-investigators and the participant enrolled in Stage 2. The participant and therapist-investigators will re-acquaint themselves with each other, and the participant will review information about MDMA-assisted therapy and all three will discuss, review and possibly revise goals for MDMA-assisted psychotherapy. The session will be recorded to audio and video. Participants may listen to or view recordings upon request.
- **Open-label MDMA session 1 (Visit 23):** The first eight-hour long open-label session with a full dose of MDMA (125 mg), **applicable for participants in Stage 2 only.** This option is not applicable to participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and 125 mg MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of their open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of 62.5 mg MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during the experimental session or after the session is over. All participants will remain overnight at the offices of Dr. Pacey. Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after Open-Label MDMA Session 1 (Visit 24):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the first open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to integrative psychotherapy sessions after experimental MDMA-assisted therapy sessions. This session will be recorded to audio and video. Participants can listen to or view recordings upon request.

- **Integrative Psychotherapy Between Open-Label Session 1 and 2 (Visits 25-26, 26.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the first and second Stage 2 open-label MDMA-assisted session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can review session recordings upon request.
- **Open-label MDMA session 2 (Visit 28):** The second eight-hour long open-label session with a full dose of MDMA (125 mg), **applicable for participants in stage 2 only.** Participants not enrolled in Stage 2 may decline to take part in this session. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants may receive copies of their open-label sessions upon request. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during or after the experimental session to remain with the participant. All participants will remain overnight at the offices of Dr. Pacey. Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after Open-Label MDMA Session 2 (Visit 29):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the second open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. The session will be recorded to audio and video, and participants can listen to or view session recordings upon request.
- **Integrative Psychotherapy Between Open-Label MDMA 2 and 3 (Visits 30-31, 31.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the second and third Stage 2 open-label MDMA-assisted session. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request. These will be the final integrative sessions for participants not enrolled in stage 2. The therapists and investigator will continue working on integrating MDMA session material into everyday life.
- **Open-label MDMA session 3 (Visit 32):** The third eight-hour long open-label session with a full dose of MDMA (125 mg) for participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive sometime during the experimental session or after it has ended or near the end of the session to remain with the participant. All participants will remain overnight at the offices of Dr. Pacey. Significant others may remain overnight with participants but do not have to do so.

- **Integrative Psychotherapy One Day after Open-Label MDMA Session 3 (Visit 33):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the third open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. This session will be recorded to audio and video. Participants can listen to or view their recordings upon request.
- **Integrative Psychotherapy After Open-Label Session 3 (Visits 34-35, 35.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval after the third open-label session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request.
- **Evaluation Six weeks after Third Open-Label Session for Participants Enrolled in Stage 2 (Visit 36):** A ninety to 120-minute visit with the independent assessor and the therapist-investigators for participants enrolled in Stage 2 occurring six weeks after the third open-label session. The independent assessor will administer the CAPS and the participant will complete the BDI and PDS.
- **Study Termination for Stage 2 Participants (Visit 37):** After completing CAPS, PDS and BDI, the participant will meet for approximately a half hour (0.5 hours) with the therapist-investigators. The participant will complete the RRPQ. Participants will discuss and reach a decision as to whether they wish to have a fourth open-label MDMA-assisted session.
- **Review and Introductory Psychotherapy Prior to Optional Open-Label Session 4 (Visit 38):** A sixty to ninety minute psychotherapy session with both therapist-investigators and participants who are going to take part in an optional fourth open-label session. This and all subsequent visits can occur for people after completing the randomized study segment or after Stage 2. **This visit and subsequent visits are applicable only to participants that the investigators determine are partial responders or nonresponders after receiving MDMA-assisted psychotherapy with the experimental dose of MDMA, either during stage 1 or stage 2 Both investigators and participants must be in mutual agreement on participant enrollment in the fourth optional open-label session.** The participant and therapist-investigators will re-acquaint themselves with each other, and the participant will review information about MDMA-assisted therapy and all three will discuss, review and possibly revise goals for MDMA-assisted psychotherapy. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. This visit and all following visits from Visit 37 onwards are only applicable to Stage 2 participants taking part in the optional open-label session.
- **Optional Open-label MDMA session 4 (Visit 39):** The fourth eight-hour long open-label session with a full dose of MDMA (125 mg). The investigator may administer a 150 and 75 mg MDMA to participants if the investigators believe it will be helpful in facilitating therapeutic response without causing harm and the participant agrees to it.

Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants may receive copies of their open-label session recordings upon request. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive sometime during or after the end of the session to remain with the participant. All participants will remain overnight at the offices of Dr. Pacey.

- **Integrative Psychotherapy One Day after Open-Label MDMA Session 4 (Visit 40):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the optional fourth open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. This session will be recorded to audio and video, and participants can listen to or view their session recordings upon request.
- **Integrative Psychotherapy After Optional Open-Label MDMA Session 4 (Visits 41-42, 42.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur after the optional fourth open-label MDMA-assisted session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video. Participants can listen to or view their session recordings upon request. Participants will schedule a visit with the independent assessor to occur two months after the fourth open-label session.
- **Evaluation Six Weeks After Optional Fourth Open-Label Session: (Visit 43):** A ninety to 120-minute visit with the independent assessor and the therapist-investigators for occurring six weeks after the optional fourth open-label session. The independent assessor will administer the CAPS, and the participant will complete the BDI and PDS. The participant will also complete the RRPQ.

## **Appendix B: Case Report Forms**

These are sample case report form drafts for the study “A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Posttraumatic Stress Disorder (PTSD)-Canada.”

The series of case report forms represents the series of events from screening up through the first experimental session of MDMA-assisted psychotherapy. The series does not include CRFs for subsequent experimental sessions or open-label sessions as the information contained is identical or nearly identical in content and format.

### **CONTAINS**

**SCREENING AND BASELINE EVALUATION  
INTRODUCTORY PSYCHOTHERAPY  
FIRST EXPERIMENTAL SESSION  
INTEGRATIVE PSYCHOTHERAPY  
FINAL EVALUATION  
MEDICATION AND ADVERSE EVENTS**



**Study Entry Criteria**

Subject screened under protocol version:  Original  Amendment # \_\_\_\_\_

Did subject meet all study entry criteria specified in the protocol  Yes  No

**If No**, please mark nature of deviation in the chart below and on the following pages

<b>Inclusion not Met / Exclusions Met</b>	<b>Criterion number (as listed in protocol)</b>	<b>Protocol deviation entry granted?</b>	<b>If yes, date granted (dd-mmm-yy)</b>
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___



**Baseline Clinical Labs Visit #1**

**Date of Result** \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_

*If any clinically significant lab results, please record in Adverse Event CRF*

*dd mmm yy*

<b>Comprehensive Metabolic Profile</b>	<b>Result</b>	<b>Unit</b>	<b>Clinically Significant?</b>
AG ratio			<input type="checkbox"/> Yes <input type="checkbox"/> No
Albumin			<input type="checkbox"/> Yes <input type="checkbox"/> No
Alkaline Phosphatase			<input type="checkbox"/> Yes <input type="checkbox"/> No
AST (SGOT)			<input type="checkbox"/> Yes <input type="checkbox"/> No
ALT (SGPT)			<input type="checkbox"/> Yes <input type="checkbox"/> No
Bilirubin Total			<input type="checkbox"/> Yes <input type="checkbox"/> No
BUN			<input type="checkbox"/> Yes <input type="checkbox"/> No
Bun/Creatinine			<input type="checkbox"/> Yes <input type="checkbox"/> No
Calcium			<input type="checkbox"/> Yes <input type="checkbox"/> No
Chloride			<input type="checkbox"/> Yes <input type="checkbox"/> No
Creatinine			<input type="checkbox"/> Yes <input type="checkbox"/> No
Globulin			<input type="checkbox"/> Yes <input type="checkbox"/> No
Glucose			<input type="checkbox"/> Yes <input type="checkbox"/> No
Potassium			<input type="checkbox"/> Yes <input type="checkbox"/> No
Protein Total			<input type="checkbox"/> Yes <input type="checkbox"/> No
Sodium			<input type="checkbox"/> Yes <input type="checkbox"/> No

<b>Urinalysis</b>	<b>Result</b>	<b>Clinically significant?</b>
Specific gravity		<input type="checkbox"/> Yes <input type="checkbox"/> No
PH		<input type="checkbox"/> Yes <input type="checkbox"/> No
Protein		<input type="checkbox"/> Yes <input type="checkbox"/> No
Glucose		<input type="checkbox"/> Yes <input type="checkbox"/> No
Ketones		<input type="checkbox"/> Yes <input type="checkbox"/> No
Occult blood		<input type="checkbox"/> Yes <input type="checkbox"/> No
Leukocyte Esterase		<input type="checkbox"/> Yes <input type="checkbox"/> No
Nitrite		<input type="checkbox"/> Yes <input type="checkbox"/> No
Bilirubin		<input type="checkbox"/> Yes <input type="checkbox"/> No
Urobilinogen		<input type="checkbox"/> Yes <input type="checkbox"/> No

<b>Thyroid Panel with TSH</b>	<b>Result</b>	<b>CS= Clinically significant</b>
Thyroxine		<input type="checkbox"/> Yes <input type="checkbox"/> No
Thyroid hormone binding ratio		<input type="checkbox"/> Yes <input type="checkbox"/> No
Thyroid Stimulating Hormone		<input type="checkbox"/> Yes <input type="checkbox"/> No
Free Thyroxine Index		<input type="checkbox"/> Yes <input type="checkbox"/> No

**Past Psychiatric Medical History**

Record any Psychiatric Diagnosis made prior to visit 1. If Diagnosis date is not known write UNK, try to provide at least a year.

<b>Diagnosis</b>	<b>Diagnosis Start date</b> mm-dd-yyyy	<b>Ongoing?</b>	<b>Stop Date</b> mm-dd-yyyy
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	



**Type and Duration of Previous Therapy**

Record any non drug therapy prior to visit 1 using the codes provided to the side of this chart. If date is not known write UNK, try to provide at least a year. Record any drug therapy on the Psychotropic Medication page.

Type	Other Therapy Type	# Sessions	Per	Start Date mm-dd-yyyy	Ongoing ?	Stop Date mm-dd-yyyy
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	

Type of Psychotherapy Code
1 = CBT (Cognitive Behavioral Therapy) 2 = Behavioral 3 = Prolonged Exposure
4 = EMDR 5 = IPT (Interpersonal Therapy) 6 = Psychodynamic
7 = Holotropic Breathwork 8 = Group Psychotherapy 9 = Other

**History of Suicide Attempts or Thoughts**

**Suicidal Tendencies:** Check the box that in your opinion most represents the frequency which the subject has thoughts of death or suicide, as determined via psychiatric interview.

- None at all
- Slight: occasional thoughts of death without suicidal thoughts
- Mild: frequent thoughts of being better off dead/occasional thoughts of suicide (without a plan)
- Moderate: often thinks of suicide or has thought of specific method
- Severe: frequent suicidal thoughts, mentally rehearsed plan, has made a suicide gesture
- Extreme: made recent preparations for serious suicide attempt
- Very

**Past Use of Ecstasy**

Has the subject ever used "Ecstasy"?  YES  NO

If Yes, # of Occasions \_\_\_\_\_

If Yes, when

- Within the last six months
- Seven to 11 months ago
- 12 to 24 months ago
- 25 to 36 months ago
- 37 to 48 months ago
- 49 to 60 months ago
- 61 months to 120 months
- Over 120 months ago.

**Past Substance Use**

Previous Alcohol Abuse/dependence  yes  no # of prior treatments\_\_\_\_\_

In the last 60 days  yes  no

***Previous Drug Abuse/dependence***  ***yes***  ***no*** # of prior treatments\_\_\_\_\_

***In the last 60 days***  ***yes***  ***no***

**CAPS Scoring – Baseline PTSD Diagnosis Visit #3** Date of Evaluation      -      -       
 mmm      dd    yy

Criterion A met (traumatic event)	Specify	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO	<b>Frequency</b>	<b>Intensity</b>
B (re-experiencing) sx (≥ 1)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
C (Avoidance) (≥ 3)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
D (Hyperarousal) (≥ 2)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
E (duration ≥ 1 month)?	Duration in Months	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
F(Distress/impairment)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
CURRENT PTSD (Criteria A-F)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
PTSD Global	Score			

Check this box if assessment occurred after screening and appropriate drug washout

**Associated Features**

<b>#25</b>	<b>#26</b>	<b>#27</b>	<b>#28</b>	<b>#29</b>	<b>#30</b>

**PDS and BDI Scoring– Baseline Visit #3**Date of Evaluation \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
mmmm dd yy**Posttraumatic Stress Diagnostic Scale (PDS) Stage 3 Outcome #1**

PTSD Diagnosis	
Symptom Severity Score	
Symptom Severity Rating	
Level of Impairment of Functioning	

**Beck Depression Inventory (BDI)**

\_\_\_\_\_ BDI score

 Check this box if assessment occurred after screening and appropriate drug washout

**Psychiatric History: SCID-Baseline diagnoses Visit #1**Date of Evaluation \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
dd mmm yy

<b>DSM Diagnosis</b>	<b>Yes</b>	<b>No</b>
PTSD		
Unipolar Depression		
Panic Disorder		
Generalized Anxiety Disorder		
Bipolar Affective Disorder-1		
Bipolar Affective Disorder-II		
Dissociative Identity Disorder		
Psychosis		
Eating Disorder		
if Yes Active Purging?		
Borderline Personality Disorder		
Substance Abuse or dependence (60 days)		
Other DSM IV diagnosis-1		
Other DSM IV diagnosis-2		

**General Well Being -Non-Experimental Sessions- Baseline**

	<b>Visit Date</b>	<b>Subject Demeanor and State of Mind</b> enter code	<b>Subject currently</b> enter code
<b>Visit #4</b>			
<b>Visit #5</b>			
<b>Visit #6</b>			

1= Very stable and calm  
 2= Stable and calm  
 3= Slightly stable and calm  
 4= Slightly distressed  
 5= Distressed  
 6= Very distressed

**A**= Does not face risk of  
 significant deterioration.  
**B**= Probably faces risk of  
 significant deterioration.  
**C**= Faces risk of significant  
 deterioration.

**Experimental Session # 1 Visit #7****Review of Inclusion and Exclusion Criteria**

Has the subject refrained from consuming prohibited food or beverages?  Yes  No

Have all meds finished tapering?  Yes  No  NA

Urine Pregnancy Test

Positive

Negative

Not Applicable (Subject is Male, Non-child bearing potential)

Urine Drug Screen

Positive

Negative

Does subject continue to meet **All Inclusion** and **No Exclusion Criteria**?  Yes  No

If No Specify \_\_\_\_\_

**Dosing**

Date \_\_\_\_\_  
          dd mmm yyyy

Record time initial dose MDMA administered \_\_\_\_\_

Record Bottle number of active placebo/ experimental MDMA \_\_\_\_\_

Second Dose of active placebo/experimental dose MDMA Administered?

Yes  No

If yes, Record time second dose was administered \_\_\_\_\_

**Record Bottle number of MDMA** \_\_\_\_\_

**Vital Signs -Experimental Session #1 Visit #7**

Mark point where supplemental dose given. Make no mark if supplemental dose not given.

Monitoring: Blood Pressure and Pulse

Postdrug (h.min)	Time	SBP	DBP	Pulse
15 min predrug				
5 min predrug				
30 min postdrug				
1 hour post-drug				
1 h 30 min postdrug				
2 h postdrug				
2 h 30 min postdrug				
3 h postdrug				
3 h 30 min postdrug				
4 h postdrug				
4 h 30 min postdrug				
5 h postdrug				
5 h 30 min postdrug				
6 h postdrug				
6 h 30 min postdrug				
7 h postdrug				
7 h 30 min postdrug				
8 h postdrug				

Temperature

Postdrug (h.min)	Time	BT <input type="checkbox"/> F <input type="checkbox"/> C
15 min predrug		
1 hour post-drug		
2 hours post-drug		
3 hrs post-drug		
4 hrs post-drug		
5 hrs post-drug		
6 hrs post-drug		

Record any additional time points here:





**SUDS -Experimental Session #1 Visit #7**

Postdrug (h.min)	Time	SUDS						
15 min predrug		1	2	3	4	5	6	7
5 min predrug		1	2	3	4	5	6	7
1 h postdrug		1	2	3	4	5	6	7
2 h postdrug		1	2	3	4	5	6	7
3 h postdrug		1	2	3	4	5	6	7
4 h 30 min postdrug		1	2	3	4	5	6	7
6 h postdrug		1	2	3	4	5	6	7
7 h postdrug		1	2	3	4	5	6	7
8 h postdrug		1	2	3	4	5	6	7

Record any additional time points here:

		1	2	3	4	5	6	7
		1	2	3	4	5	6	7
		1	2	3	4	5	6	7
		1	2	3	4	5	6	7

**Integrative Psychotherapy After Experimental Session #1 (Visit 8)****Subject Belief of Condition Assignment Visit #8**

Indicate what condition the subject believes they were assigned

- Low dose MDMA
- Experimental Dose MDMA

Indicate the subject's certainty about this belief of condition assignment

- Not at all certain
- Somewhat certain
- Certain
- Very certain

**Spontaneously Reported Side Effects Post Experimental Session #1 Visit #7-9**

Please record the maximum intensity of any spontaneously reported effects for 7 days after drug administration.

Report Duration for the first 24 hours.

Visit/Day	Visit 7 Day 0	Visit 7 Day 0	Visit 8 Day 1	Phone Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Duration in hours	Intensity	Intensity	Intensity	Intensity	Intensity	Intensity	Intensity	Intensity	Intensity
Report Max Intensity for the 24 hour period  0= None Reported 1= Mild 2= Moderate 3= Severe	Report Duration to the nearest 1/2 hour for the first 24 hours only									
Check None if no symptoms are reported for the 24 hour period	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None
Anxiety										
Difficulty Concentrating										
Dizziness										
Drowsiness										
Dry mouth										
Fatigue										
Headache										
Heavy legs										
Impaired gait/balance										
Increased irritability										
Increased private worries										
Insomnia										
Jaw clenching, tight jaw										
Lack of appetite										
Low mood										
Nausea										
Need more sleep										
Nystagmus										
Parasthesias										
Perspiration										
Restlessness										
Sensitivity to cold										
Thirst										
Weakness										

**General Well Being Visit #8-10**

**Complete at Visit 8;** Since the Experimental Session at Visit 7 the subject has:

worsened       remained pretty much the same       improved

	Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
<b>Visit # 8</b>			
<b>Phone Day 1</b>			
<b>Phone Day 2</b>			
<b>Phone Day 3</b>			
<b>Phone Day 4</b>			
<b>Phone Day 5</b>			
<b>Phone Day 6</b>			
<b>Phone Day 7</b>			
<b>Visit #9</b>			
<b>Visit #10</b>			

1= Very stable and calm  
 2= Stable and calm  
 3= Slightly stable and calm  
 4= Slightly distressed  
 5= Distressed  
 6= Very distressed

**A=** Does not face risk of significant deterioration.  
**B=** Probably faces risk of significant deterioration.  
**C=** Faces risk of significant deterioration.

**Additional Non-Drug Psychotherapy**

Check this box if the participant did not schedule any additional non-drug psychotherapy sessions in the period between Visit 8 and Visit 10. If this box is checked, then draw a diagonal line through the page. If any additional non-drug psychotherapy visits were scheduled, complete general well-being ratings for all additional visits and draw diagonal lines through any empty rows. Label each additional non-drug psychotherapy session with a fraction after 10, using consecutive numbers for each session (as 10.1, 10.2, etc).

**Number of additional Visits = \_\_\_\_\_**

**General Well Being**

	Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit 10.__			
Visit 10.__			
Visit 10.__			
Visit 10.__			
Visit 10.__			
Visit 10.__			

**1=** Very stable and calm    **A=** Does not face risk of significant deterioration.  
**2=** Stable and calm        **B=** Probably faces risk of significant deterioration.  
**3=** Slightly stable and calm    **C=** Faces risk of significant deterioration.  
**4=** Slightly distressed  
**5=** Distressed  
**6=** Very distressed

**Final Evaluation (Visit 19)**

**CAPS Scoring – PTSD Diagnosis Visit #19**

**Date of Evaluation** \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
 dd mmm yy

Criterion A met (traumatic event)	Specify	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO	<b>Frequency</b>	<b>Intensity</b>
B (re-experiencing) sx ( $\geq 1$ )?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
C (Avoidance) ( $\geq 3$ )?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
D (Hyperarousal) ( $\geq 2$ )?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
E (duration $\geq 1$ month)?	Duration in Months	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
F(Distress/impairment)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
CURRENT PTSD (Criteria A-F)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
PTSD Global	Score			

**Associated Features**

<b>#25</b>	<b>#26</b>	<b>#27</b>	<b>#28</b>	<b>#29</b>	<b>#30</b>

**Final Evaluation (Visit 19)**

**PDS and BDI**

**Date of Evaluation** \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                  dd  mmm  yy

**Posttraumatic Stress Diagnostic Scale (PDS)**

PTSD Diagnosis	
Symptom Severity Score	
Symptom Severity Rating	
Level of Impairment of Functioning	

**Beck Depression Inventory (BDI) Visit #15**

\_\_\_\_\_ BDI score

**RBANS- Evaluation Visit #19**

**Date of Evaluation** \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
dd mmm yy

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

<b>RBANS</b>	<b>Index Score</b>	<b>%ile</b>
Immediate Memory		
Visuospatial/Constructional		
Language		
Attention		
Delayed Memory		
Total Scale		

**Paced Auditory Serial Addition Task (PASAT) – Baseline Visit #4**

<b>PASAT</b>	<b>Raw</b>	<b>%ile</b>
1		
2		
3		
4		
Total		



**General Well Being Visit # \_\_\_\_\_ (16, 26, 35)**

	Visit Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
<b>Visit # 19</b>			

- 1= Very stable and calm
- 2= Stable and calm
- 3= Slightly stable and calm
- 4= Slightly distressed
- 5= Distressed
- 6= Very distressed

- A=** Does not face risk of significant deterioration.
- B=** Probably faces risk of significant deterioration.
- C=** Faces risk of significant deterioration.

Please check only one  Visit 20 (End Randomized )  
 Visit 37 (End Stage 2)  Visit 43 (Optional Open Label Stage 1 / Stage 2)

**Reactions to Research Participation Questionnaire (RRPQ)**

Please write in the numbers corresponding to the three top-ranked reasons for participating (the numbers to the left of each reason on the form. Write the number “1”, “2” or “3”) for each reason.

_____ 1. I was curious	_____ 4. I don't know	_____ 7. For the money
_____ 2. To help others	_____ 5. Thought it might improve my access to health care	_____ 8. I didn't want to say no
_____ 3. To help myself	_____ 6. Felt I had to	_____ 9. Other: _____ _____

Please write in the scale scores the RRPQ below.

- 1. Participation                    1 \_\_\_\_\_
- 2. Personal Benefits            2 \_\_\_\_\_
- 3. Emotional Reaction          3 \_\_\_\_\_
- 4. Perceived Drawbacks        4 \_\_\_\_\_
- 5. Global Evaluation            5 \_\_\_\_\_



Subject Number \_\_\_\_\_

CRF DRAFT

Visits 3 through Termination

PI: Pacey, I.

Concomitant Medication CRF

Page X1 Series \_\_\_\_ √ if Last Page

**Non Psychotropic Concomitant Medications**

At Visit 3 record all non psychotropic medications currently being taken and check the prestudy box (include start date if known) Provide diag# (from Med Hx page). Record all new prescription and non-prescription non psychotropic medications taken after visit 3 through termination visit. Provide AE# (from AE page) or other Reason for Treatment. Check the continuing box if continuing at study termination.  **CHECK IF NONE**

Medication	Route	Dose	Start Date (dd/mmm/yy)	Stop Date (dd/mmm/yy)	Reason for Treatment Complete at least one column		
					Med HX Diag #	AE#	Other
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			

Subject Number \_\_\_\_\_

CRF DRAFT

Visits 3 through Termination

PI: Pacey, I.

Psychotropic Medication CRF

Page X2 Series \_\_\_\_\_ ✓ if last page

**Psychotropic Medication and Tapering**

- Record psychotropic medications previously used **and** psychotropic medications subject is on at visit1. Check the Prestudy box (include start date if known) and provide Disorder Code. Check Tapered box for medications tapered from V2 or V3. Provide route, dose and stop date for all medications.
- Record **all new psychotropic medications** taken after visit 1 through termination visit. Provide route, dose and start date. Provide AE# (from AE page) and check Rescue box if used as a rescue medication or complete Other Reason for Treatment. Check the Continuing box if continuing at study termination.  **CHECK IF NONE**

Medication	Route	Dose	Start Date (dd/mmm/yy)	Stop Date (dd/mmm/yy)	Reason for Treatment Complete at least one column		
					Prestudy Disorder Code#	AE#	Other
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	

**\*Code for prestudy disorders**

- 1 = Depression
- 3 = Panic Disorder
- 5 = Pain management (PRN)
- 7 = Obsessive-Compulsive Disorder (OCD)

- 2 = Anxiety
- 4 = Pain management (routine)
- 6 = Illness-related anxiety
- 8 = PTSD

Subject Number \_\_\_\_\_

CRF DRAFT

Visits 3 through Termination

PI: Pacey, I.

Psychotropic Medication CRF

Page X2 Series \_\_\_\_\_ √ if last page

**Adverse Events**

CHECK IF NONE

AE #	Adverse event Diagnosis	Serious? a	Onset date (dd/mmm/yy)	Resolution date (dd/mmm/yy)	Severity b	Frequency c	Action taken for Study d	Action taken- treatment e	Action Taken Other Specify	Outcome	Relationship to Drug g

a  
**Serious?**  
1 = Serious\*  
2 = Not serious

\* Serious = Fatal, life-threatening, requires prolonged hospitalization, results in persistent or significant disability, or requires medical or surgical intervention to prevent one of the outcomes defined as "serious" listed above.

b  
**Severity**  
1 = Mild  
2 = Moderate  
3 = Severe

c  
**Frequency**  
1 = Single/Intermittent  
2 = Continuous

d  
**Action Taken: Study**  
1 = None  
2 = Interrupted session  
3 = Delayed experimental session  
4 = Discontinued experimental session  
5 = Removed from study

e  
**Action Taken: Treatment**  
1 = None  
2 = Procedure or therapy  
3 = Blood or Blood products  
4 = Withdrawn from study due to AE  
5 = Prescription Med  
6 = Non Prescription Med  
7 = Hospitalization  
8 = IV Fluids  
9 = Other specify

f  
**Outcome**  
1 = Full recovery/return to baseline  
2 = Persists, diminishing  
3 = Persists, worsening  
4 = Persists, the same  
5 = Alive with sequelae  
6 = Death

g  
**Relationship to Drug**  
1 = Not related  
2 = Possibly related  
3 = Probably related

