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 approximately five to fifteen 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 be attended 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.

Participants will also complete a self-report measure of suicidal ideation, the ASIQ, after undergoing integrative psychotherapy on the day after each experimental or open-label session.

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
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.

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.
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.

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.
Additional adverse events collected for seven days after each experimental session are:
• Common side effects.
• Exacerbation of anxiety.

Medical Monitor:

Study Monitor:

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:
- Study Monitor:

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. 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.

**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-γ 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 antiretrovirals 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 nonmedical 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; Mollière et al. 1990; Sabol et al. 1995; Seiden and Sabol 1996). Previous studies in nonhuman primates overestimated human-equivalent doses (Meachan 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 audiotape 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 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.
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

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-methylenedioxymethamphetamine HCl, also referred to as N-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula C₁₁H₁₅N₂O₂. 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 2005.99) 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 from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by Prof. DCR, University of Bern, Switzerland. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no. with no decomposition products detectable and a HPLC purity >98%.

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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 5HT1A receptors and elevating the neurohormone oxytocin (Thompson et al. 2007). Studies in rats reported that stimulating 5HT1A receptors attenuated aggression, and administering a 5HT1A 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 5HT1A receptors (Thompson et al. 2007). Pre-administration of the 5HT1A and β 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 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 Brodkin 1991; Rudnick and Wall 1992; Schuldiner et al. 1993). Direct MDMA stimulation of postsynaptic 5-HT2A receptors and α2 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-HT2A receptors on GABAergic striatonigral neurons (Yamamoto et al. 1995).

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.
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_2 antagonist haloperidol decreased positive mood and increased anxiety after MDMA, suggesting that indirect stimulation of D_2 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 5HT₂B and α₂ 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 M₃ or H₁ receptors. 5HT₂B receptors in the medial amygdala may contribute to the anxiolytic effects of MDMA, as may also be true for the serotonin releaser and 5HT₂B agonist fenfluramine. Direct MDMA stimulation of postsynaptic α₂ adrenoceptors may also help individuals remain emotionally calm despite noradrenergic activation, as with related α₂ agonists clonidine and guanfacine, possibly through altering the balance between α₁ to α₂ stimulation (Franowicz and Arnsten 1998).

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

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ki (mM)</th>
<th>Hot Ligand</th>
<th>Species</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin transporter</td>
<td>0.072 or 0.102</td>
<td>Functional (1), 3H-citalopram (2)</td>
<td>Rat, Human Brain, Cloned</td>
<td>(Jones et al. 2004; Setola et al. 2003)</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine Transporter</td>
<td>0.110</td>
<td>Functional</td>
<td>Rat</td>
<td>Brain</td>
<td>(Setola et al. 2003)</td>
</tr>
<tr>
<td>Dopamine transporter</td>
<td>0.278</td>
<td>Functional</td>
<td>Rat</td>
<td>Caudate</td>
<td>(Setola et al. 2003)</td>
</tr>
<tr>
<td>5HT₂B</td>
<td>0.5 or 0.7</td>
<td>3H-LSD</td>
<td>Human</td>
<td>Cloned</td>
<td>(Setola et al. 2003), (PDSP 2007)</td>
</tr>
<tr>
<td>α₂C</td>
<td>1.12</td>
<td>3H-Clonidine</td>
<td>Human</td>
<td>Cloned</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>Calcium Channel</td>
<td>1.2</td>
<td>3H-Nitrendipine</td>
<td>Rat</td>
<td>Heart</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>α₂B</td>
<td>1.8</td>
<td>3H-Clonidine</td>
<td>Human</td>
<td>Cloned</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>M₁</td>
<td>1.8</td>
<td>3H-QNB</td>
<td>Human</td>
<td>Cloned</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>H₁</td>
<td>2.1</td>
<td>3H-Pyrilamine</td>
<td>Human</td>
<td>Cloned</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>α₂A</td>
<td>2.5</td>
<td>3H-Clonidine</td>
<td>Human</td>
<td>Cloned</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>M₃</td>
<td>6.3</td>
<td>3H-QNB</td>
<td>Human</td>
<td>Cloned</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>M₄</td>
<td>8.2</td>
<td>3H-QNB</td>
<td>Human</td>
<td>Cloned</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>5HT₂A</td>
<td>8.3</td>
<td>3H-ketanserin</td>
<td>Rat</td>
<td>Cortex</td>
<td>(Lyon et al. 1986)</td>
</tr>
</tbody>
</table>

**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 D2 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 D2 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 5HT2A 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 5HT2A 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 5HT2A receptor antagonist ketanserin reduced elevated diastolic pressure (Liechti et al. 2000b), while the D2 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 adrenocorticotropic 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 (Pacifici et al. 2001b). Harris and colleagues failed to
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

Studies conducted in Spain suggest that MDMA acutely affects the immune system (Pacifici et al. 2000; Pacifici et al. 2001a; Pacifici 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 proinflammatory cytokine interleukin 2 (IL-2) and increased levels of the immunosuppressive and anti-inflammatory cytokine interleukin 10 (IL-10) (Pacifici et al. 2004; Pacifici 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 (Pacifici 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 α 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 (Pacifici 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 ± 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 (Ochen 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 (Huijzin 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 (Dykhuizen 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; Meehan 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 \([^{11}C]McN5652\) 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-naive 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, parasthesias (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,
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 ± 14.1 per hr, while renal clearance was 13.0 ± 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.

**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 ± 14.1 per hr, while renal clearance was 13.0 ± 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
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.
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). $C_{\text{max}}$ was $232.9 \pm 39 \, \mu g/L$, AUC$_{0-24}$ was $2564 \pm 762 \, \mu g/\text{h}/L$, $T_{\text{max}}$ was $25.5 \pm 0.33 \, \text{h}$, and AUC/dose was $25.64 \pm 7.6 \, \mu g/\text{h}/(1*mg)$. 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 $T_{\text{max}}$.

**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 α-methylpseudopine), 3,4-dihydroxyamphetamine (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; Delaforgue 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
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 demethylation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylation, including CY1A2 and CYP3A4.
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

Acute toxicity

Acute toxicity is described above in “Safety Pharmacology”, including both common side effects and effects occurring in ecstasy users. The estimated LD_{50} 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_{50} 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
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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